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LANGLEY PORTER BIRTHDAY NUMBER

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THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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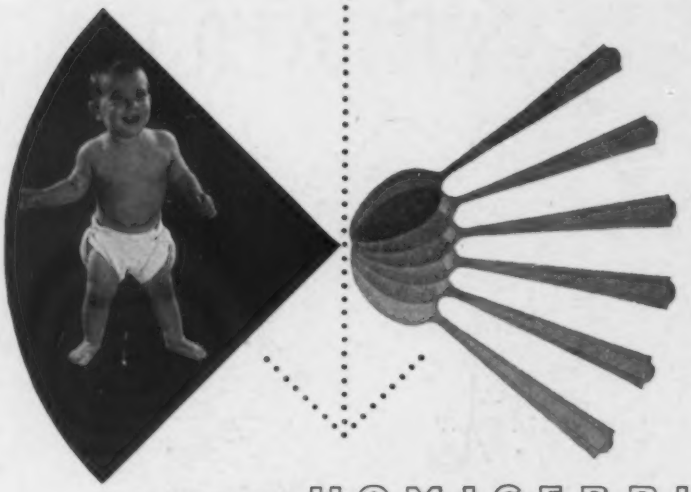

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LANGLEY PORTER, M.D.

The Journal of Pediatrics

VOL. 37 OCTOBER, 1950 NO. 4

Langley Porter Birthday Number

LANGLEY PORTER

TO VOICE an adequate appreciation of Dr. Langley Porter, whether as a leader in his profession or as a friend and companion, without committing plagiarism, is most difficult. More baffling still, the intellectual caliber of the company the good doctor keeps renders illusory any hope that one may enhance the tributes from these many and varied sources which are so richly his due.

The Langley Porter Clinic Building at the University of California Medical Center in San Francisco is a testimonial to the quality and character of Dr. Porter's services to the science and art of medicine and to the welfare of humanity, uniquely eloquent: for rarely do men acknowledge their debts of respect and affection while the individual is still alive and able to enjoy thoroughly the tribute that is paid him. But the story of the Clinic and its dedication is a twice-told tale.

Perhaps the only comment one may offer about Dr. Porter that has not too often been repeated is that he was born on January 30, 1870, and is this year celebrating the eightieth anniversary of his birth. Three-quarters of a century of dynamic living, and going strong on the fourth! It is this, therefore, on which I choose to congratulate him, at the same time that I look askance at the arbitrary nature of chronologically set retirement regulations. In a less "regulated" age, Dr. Porter's usefulness as a physician would have received progressively greater recognition with each passing year, because his health and longevity would have clearly demonstrated that he knew the secret and had the "power." But we retired him at the age of seventy!

The sick of today, even as the sick of past yesterdays, seek for the physician who, above and beyond professional competence, possesses the understanding heart, the intuitive insight, the "power and the virtue" (as it is phrased in the Gospel of Mark) to create an all-encompassing confidence. Here we begin to approach the core of Dr. Porter's skill as a physician, I believe, for there have been many times, while in his company, that I have found it impossible even to think of being ill. I look forward to many more such occasions, not to the end of his days but to the end of mine.

ROBERT G. SPROUL

DEAN'S SALUTATION

THIS issue of the Journal of Pediatrics is a particular tribute to Langley Porter in recognition of his eightieth birthday. To the people, to the pediatricians on the Pacific Coast, and to medical educators, it is an opportunity to recognize the contributions of a man of great talent who in many ways is of pioneer stuff. He has endeared himself in the annals of San Francisco history by his leadership in welfare and civic affairs. As perhaps the first to salvage the care of children from neglect or misunderstanding, he has been the mentor in the pediatrics field on the Pacific Coast; and in medical education, he has maintained that balance of classical culture and scientific and humanitarian acumen that is our professional and educational tradition and heritage.

In his vigor and alertness of today, we are grateful for having his leadership and example.

FRANCIS SCOTT SMYTH, M.D.

LANGLEY PORTER

W. E. Carter, M.D.
San Francisco, Calif.

IT HAS never been a man's fortune to choose that period of the world's existence in which he might live, but had one that option, how could he chose a more fortuitous period than that golden era of science and medicine that fell between 1870 and the present time? And it has been in that fateful period of the world's development that Langley Porter has lived.

One can best visualize, indeed dramatize, that span of time, by recalling, decade by decade, the world-shaking events which came to life in the scientific sphere as this boy grew up, matured, and has now reached the rich age of eighty.

It was during his years that Hansen discovered the leprosy bacillus, Lister the concept of sepsis and antisepsis, based on the work of Pasteur, that great investigator who in the 1860's had made the first immunological moves since Jenner in 1796, and who later worked with fowl cholera, anthrax, and eventually with rabies and its vaccine.

During his early manhood came the discovery of the bacterial causes of disease (thanks to Hesse's discovery of agar as a growth medium), the tubercle bacillus by Koch, the typhoid bacillus by Eberth, the diphtheria bacillus by Klebs and Loeffler, and a dozen others. What a revolutionary effect these astounding events must have had on an active and plastic mind. Could any period in the world's history have been more favorable to the development of new concepts, inspirational dreams of human betterment, and driving resolves for fresh action, on the part of a young man of twenty, just beginning his medical career?

The decade of his twenties can well be called the period of the filtrates: bacterial toxin was discovered by von Behring and Kitosato, filterable viruses were found, first in plants and then in animals, and Buchner's zymase became the center of bacterial interest.

During his thirties the world pooled its efforts to uncover the cause of syphilis, and establish the complement-fixation test, without which the discovery of the spirochete would have meant little. Theobald Smith unlocked the door for the recognition of anaphylaxis, and Nicolle put his finger on the epidemiologic clue in typhus fever.

During Porter's forties, Bela Schick's famous test was followed up with toxin-antitoxin mixture for diphtheria; and then came typhoid vaccine. Meanwhile rickettsiae came into the range of view, and Carrel pioneered the way for later developments in tissue culture by cultivating the hearts of chickens.

From fifty to sixty he saw BCG launched on its still unfixed path; the bacteriophage idea developed; and Fleming noted the idea which was to lead to penicillin years later.

From the Outpatient Department, University of California Hospital.

The decade beginning with his sixtieth year saw the dread pneumococcus subdued by the sulfonamide drugs; and the electron microscope offered the first visual advance since the Abbe condenser, and added impetus to the growing art of isolating and cultivating viruses.

The period 1940 to 1950 will be remembered as the decade of the antibiotics. Just as Pasteur had observed that alcohol was the product of growth of microorganisms, so were the antibiotics, the by-products of growth—and they soon took a prominent place in the microcosmic chemical factories. And parenthetically, let us hope that it will not be the jumping off place for a wild melee of research racketeering and financial exploitation of the sick.

The preceding thumbnail sketch of the period which Jordan called, "The Years of a Man," gives a fleeting glance of the kaleidoscopic scene covering the pregnant years corresponding to the life of Langley Porter. Prognostication is hazardous, but it is difficult to see how any other era can be so significant, for we must recall that during that time, scientific medicine, starting from scratch, has moved from a darkened world of empiricism and dogma, to one of rationalization through controlled experiment. And the stature of Langley Porter was one to match that great progress in medicine.

Langley Porter was born in Montreal on January 30, 1870. Orphaned at four, he was adopted by his mother's sister and her husband, Walter Drake. This brought the child into a home atmosphere in which medicine was a constant influence, for Drake's brother, Joseph Morley Drake, was Professor of the "Institutes of Medicine" at McGill University. The "Institutes" covered instruction in all those subjects now classed as "pre-clinical." The undergraduate, William Osler, became a student-assistant of Drake, and after his graduation, continued the relationship as an instructor, only to succeed the older man as professor. During all these years, young Osler was a frequent visitor in the Drake home; and the young boy, as he grew up, felt the coming master's charm, as he heard the grown-ups discuss Willie's brilliance and goodness, and the probable great future in store for him. All these things made a profound impression on the growing boy—an impression which has never faded. He was too young to work directly under that outstanding physician of modern times, but these youthful associations, together with occasional contact in later life, and a passionate reading of Osler's writings, made him a devotee of that great westerner who did more than any other person to make the New World medically conscious. Early upbringing in hands steeped in middle-class British tradition, homes where God and Queen Victoria were effective members of the family, created bonds of sympathy and understanding that never weakened; and memories of the conversations of the Drakes and Osler, in later years, heightened the student's enjoyment of the master's works. Many years afterward, the young medical man, with Osler's help, was enabled to work in London under Stephen McKenzie, Henry Head, and Robert Hutchinson, inspiring clinicians all, and then under Arthur Kieth, anatomist, and James Bullock, bacteriologist, scholars unexcelled in their fields. Hutchinson, pediatrician and pioneer in nutrition, left an indelible influence on the young

Canadian, who later rounded out his studies by working in Paris with Comby and in Germany with Czerny—all acknowledged as leading pediatricians of the time.

Before undertaking the study of medicine, Langley Porter acquired a Bachelor of Science degree in Chemistry at the Pennsylvania Military College; and he began his self-support as a teacher in chemistry at St. Mathew's Private High School in San Mateo, California. While there he organized a cadet corps, and developed baseball and football teams. In 1894, he entered Cooper Medical College in San Francisco, now the medical department of Stanford University, where he was employed as student assistant in chemistry. Because of credits allowed in view of his degree of Bachelor of Science, he graduated in 1896. Then followed a year of internship at St. Luke's Hospital in San Francisco. The contact, during those years, with men like Levi Lane, Farnum, Steele Cheney, Stanley Stillman, and Emmett Rixford at Cooper, and with D'Evelyn Dodge, and George Shields at St. Luke's, learned doctors and great teachers, all of them, left an indelible impression to his approach to clinical medicine.

Following his internship came a voyage to Manila, as transport-surgeon on the City of Para, the ship which carried the 13th Minnesota Volunteers, a regiment that distinguished itself in the conquest of the Philippines.

In 1899 to 1904, followed more European experiences, and the return to San Francisco with wife and child. It was natural then that the rapidly developing field of pediatrics should attract his attention. Because of the incidence of diphtheria, scarlet fever, measles, and chicken pox, the way was opened for him, in 1905, to become City Physician for Communicable Disease. Among these smallpox, leprosy, plague, and typhus presented themselves from time to time. After the earthquake and fire of 1906, communicable disease problems became formidable. Because of the administrative capacity of the late James Ward, President of the San Francisco Board of Health, with whom Porter worked constantly, the alarming situation was kept in hand. It was during this difficult period that the political scandals of the Schmitz-Ruef regime became intolerable and these were resolved only when the ring was broken up and the leaders jailed. At the height of all these events, plague appeared, and the City Health Administration called on the help of the Public Health Service of the Federal Government. The Kitosato plague resistance plan had been advocated by Porter and adopted by Ward, and was in operation when Colby Rucker and Rupert Blue took over in behalf of the United States Public Health Service. With very few modifications it was continued until the campaign came to an end with the situation controlled. These activities aroused in Langley Porter a conviction of the importance of public health measures, and brought about his keen and continuing support of the San Francisco Health Department, which under William C. Hassler and later, his devoted friend, J. C. Geiger, has grown to an outstanding institution in American health organization.

Teaching had always appealed to Langley Porter as an essential part of the physician's duties—teaching of students, teaching of laymen, the latter

almost as important as the former. His undergraduate activities in pedagogy began as a prep school instructor in chemistry, continued as student instructor at Cooper, and after graduation, he established a pediatric department at the San Francisco Polyclinic.

In 1907, Langley Porter took over the Children's Clinic of what was then Cooper Medical College. This had been organized during the late nineties by William Fitch Cheney, an inspiring teacher, whose influence on the young medical student had been great. Cheney had developed at the same time a strong out-patient medical clinic which absorbed his major interest. This left the pediatric division in the hands of Porter, under whose direction, aided by such enthusiasts as Romilda Meade, Herbert Yerrington, Florence Holzclar, and Arthur Ritter, it became a full-fledged department of teaching. In this department Ritter organized and carried on the earliest psychological clinic for children in the west and Matilda Gates studied the development of adolescent girls. With Ernest Chipman, Porter demonstrated that papular urticaria follows sensitization by flea bites, while pigmented urticaria results from bedbug sensitivity.

It is natural that Langley Porter, as a student of Henry Head, should have had a strong interest in neurology and its corollary psychiatry, which bloomed somewhat later. Poliomyelitis, tuberculosis of the brain, central nervous system syphilis, and brain tumors particularly excited his interest, both at Stanford and at the Hospital for Children.

He developed a sort of a private clinic in his own office. During those early days of pediatrics, specialists were not common, and as a result, patients came to him from all over the western states, Mexico, and the Orient. Throughout the many years of his practice of pediatrics in San Francisco, his office was always open to physicians and there was seldom a time when one, two, or even three medical visitors were not in attendance, some of them for months on end. His patients accepted this, and did not object, after his gracious introduction of the visitor as "my associate." His two or three assistants looked upon him as their elder brother, listened to his gentle admonition when they failed, or glowed in his approbation when they succeeded. His kindly smile of appreciation was compensation enough for long hours of overtime and night work in this most demanding of all the specialties. Numerous middle-aged, even elderly physicians, now eagerly confess that their ideals and attitudes stem from this source.

Langley Porter was the first physician of the Far West to be invited to membership in the American Pediatric Society. Before this group he read numerous papers. He wrote extensively, both individually, and in collaboration with his associates, mostly on the subject of infant nutrition. Early he abandoned "percentage" feeding and urged the balanced diet, the computation of intake in terms of calorie, protein, carbohydrate, and mineral needs. His interest in scientific medicine was rewarded by the presidency of the San Francisco Medical Society in 1910. His work in clinics and with the problems of the less affluent led him to advocate some system of medical prepayment insurance that would cushion the disaster of illness, the plan to be promulgated by the pro-

fession itself. For years, in and out of season, he urged this on his colleagues, and while he was not in any way connected with the development of the California Physician's Service, its formation was a source of great satisfaction to him.

Early in his practice, it became evident to Porter that sick children generally were not getting to the full all that was then known of modern pediatric art. The great majority were being treated by general practitioners, many of whom frankly admitted their inadequacy, and longed for enlightenment. At the request of the publishers of the JOURNAL, he, in collaboration with a young general practitioner, undertook the codification of known and accepted practices in pediatrics in a book designed largely for the general doctor and the intern, *The Management of the Sick Infant and Child.* Before it was completed the volume reached, including the illustrations, some 700 pages, somewhat to the dismay of the publishers. But fortunately their apprehensions proved groundless, for during the next twenty years, the book went through six editions and circulated both in this country and abroad.

Late in 1924, the stress of large practice, together with the results of illness, made a long vacation imperative. A sea voyage led to a three-year Italian holiday, during which time he continued his medical interests and, as well, indulged in a long-held desire to examine closely the Renaissance and classical cultures at first hand. As a result, his enthusiasm for the history of medicine was greatly reinforced. During this period an offer came of the Deanship of the University of California School of Medicine, and this was accepted. After an intensive study of the leading medical schools of Europe and of America, he returned to San Francisco to begin an association with colleagues and students which was to continue with great satisfaction for fourteen years. Continuing the tradition, inherited from such great clinicians as William Watt Kerr, Herbert Moffitt, Wallace Terry, and Saxton Pope, every effort was made to develop the curriculum in the direction that might produce practitioners of the highest competence. With able men occupying the chairs of medicine, surgery, obstetrics and gynecology, pediatrics, and of the physical sciences as well, and with a host of enthusiastic young colleagues, the accomplishment of this aim was greatly facilitated. The physical plant and equipment of the medical school were inadequate, but through the understanding and support of President Campbell of the university and the regents, funds were acquired for reconstruction and extension; and by 1930, room was found in the original medical school building for the Departments of Bacteriology, Pharmacology, Pathology, Clinical Anatomy, Preventive Medicine, and the Student's Health Service. These changes were followed in 1936 by the construction of a new Out Patient Department building. This permitted the vacating of the first, second, and third floors of the crowded old building which had been employed for this purpose. It is interesting to note, during the present inflationary period, that the cost of the entire new building, seven stories in height, was something less than one-half million dollars. The enthusiastic support of the medical school as a part of the university by President Campbell was continued and augmented by his successor, President Sproul. Indeed, after Dean Porter's

retirement, the latter actually came to the San Francisco campus, and acted as dean for several months, much to the advantage of the School of Medicine. This experience perhaps impressed on the president the now commonly held judgment that few universities are greater than their medical schools. The completion of these extensions and the fine cooperation between the faculties in Berkeley and faculty at San Francisco, produced the policy, that while clinical teaching is paramount, a background of research is imperative if instruction is to be adequate. Here the help of Professor Leuschner of the Graduate Division was of greatest importance. He served as a coordinator and among the holders of divergent opinions, and in the end, brought about effective cooperative action.

The school had begun as a proprietary institution, the Toland Medical College, and had been taken over by the university under President Gilman in 1873, but only nominally. The university authorities were slow to provide financial support. But under the administrations of President Campbell and of President Sproul, things became very different. Experimental surgery was established and adequately housed in a building, built specifically for the purpose. Pharmacological research, under Chauncey Leake, became more and more active, offering opportunity for medical school workers, operating closely with students of allied departments on the Berkeley campus. The need for an expanded division of clinical anatomy and its representation in the teaching of upper classmen became apparent. Thanks to the efforts of Herbert Evans, the services of John Saunders, a young and tireless Fellow of the Royal College of Surgeons, Edinborough, was secured; and through his cooperation the Department of Surgery, particularly its orthopedic division, was strengthened. Karl Meyer's help in setting standards for research and teaching was inestimable.

A Department of Pediatrics had been developed in the medical school largely because of the enthusiasm and industry of William B. Lewitt, and was in active operation in 1913, when the service of a young Harvard pediatrician, William Palmer Lucas, was acquired. Lewitt's enthusiasm for preventive pediatrics was shared by Porter, who was then Associate Clinical Professor. On Lucas' retirement in 1932, Francis Scott Smyth, present Dean of the School of Medicine, was made Professor. In 1942, William C. Deamer became the active head of the department and serves in that capacity at this time.

Under Sanford Larkey a sound Department of Medical History and Bibliography was inaugurated. A call to Johns Hopkins came to Larkey where he still administers the William Welch Library succeeding Fielding Garrison as librarian. He was followed by Chauncey Leake and John Saunders, and under the direction of this trio, a magnificent library, including a fine rare book collection, was adequately housed.

Among the policies initiated by Langley Porter, none have been more fruitful than the Referred Service. In the late twenties, it became apparent that the routine out-patient attendance supplied an insufficient number of cases of teaching value. It was decided thereupon to ask for the cooperation of the medical profession throughout the state. Doctors were invited to send problem patients for adequate study from among those whom they believed were unable

to afford the fees, properly asked by private consultants. These patients are given a thorough study in the various departments, and complete reports are sent to the referring doctors and the patients returned to their care. In this manner a full service is provided for the patient, and at the same time, real aid is given to the referring practitioner. The staff and students of the medical school are given insight into the doctor-patient relationship and, as well, an understanding of the delicate problems involved in consultation. That the original idea was sound, has been proved by the fact that the number of referred patients at the present time exceeds 6,000 annually.

As a pediatrician the dean had long been interested in behavior problems of children and he was convinced of the soundness of Freud's theory that the genesis of many adult neuroses lay in the mismanagement of such crises during childhood and adolescence. He was particularly troubled because in the twenties and early thirties, these aspects of disease received so little attention from medical men and too little consideration in medical education. Furthermore, experience with the state hospitals of the time distressed him beyond expression. It was his belief that a closer liaison between psychiatry, neurology, and clinical medicine on the one hand, and biological and clinical research on the other, would vastly benefit the medical profession and the society it serves. This idea found ready acceptance among members of the faculty, and it found also the active support of Harry Lutgens, then Director of the State of California Department of Institutions (now the California State Department of Mental Hygiene). It seemed that the most practical approach would be to erect a hospital clinic with an out-patient department and research laboratories under the combined authority of the state and of the university. The state legislature was approached, and without a dissenting vote, appropriated two million dollars; but alas, Governor Merriam, no friend of medicine, pocket-vetoed the bill, and the plans lay useless in the medical school files, there to remain, until a later executive, Governor Olsen, appointed Aaron Rosanoff as Director of Institutions. Rosanoff, a psychiatrist of national reputation, accepted and supported the idea, the legislature again made the appropriation, and the present psychiatric institution was erected and dedicated at an impressive ceremony. It was hoped that studies to be done in this clinic would eventually bring about a solution to some of the many problems pertaining to psychiatric care in the state's hospitals for the treatment of mental diseases. It was planned to strengthen and extend the existing parole service. This service was designed to function through out-patient departments, stemming from the parent clinic but located in various parts of the state. Even more important is the policy of the preventive aspects of mental disease. It is gratifying to observe that within this first decade of the program, many of its objectives are being achieved. In addition to this, modern methods of the care of psychiatric patients have developed under the far-sighted direction of Karl Bowman and his associate, Alexander Simon, both excellent teachers. It is noteworthy that this is the first instance in California of two separate, similar state departments, so often jealous of each other's prerogatives, coming together in continuing operation for a common good; and too much credit cannot be

given to the then Attorney General Kenney and his Assistant Attorney General Coakley who, working with the indefatigable University Comptroller Corley, did so much to bring about this happy conclusion.

By the time the Psychiatric Clinic was an accomplished fact, years had accumulated and brought the dean to the age of retirement. The University granted him emeritus standing and awarded him an honorary LL.D. However, his interest in the School of Medicine and Psychiatry, particularly juvenile psychiatry, did not flag. The authorities of the state and the Regents of the university, casting about for a name for the new institution, decided to call it the Langley Porter Clinic. So it happened that a psychiatric institute came to bear a name previously tied to pediatrics.

In the years since it has been a source of deep gratification to this physician and educator, to see the great advances made by the psychiatric clinic, under an imaginative and scholarly direction. He has perceived also the steady progress of the medical school to an envied place among the medically great, under the administration of Francis Smyth, himself an eminent pediatrician. If asked to explain the steady rise of the School of Medicine and its increasing influence in academic circles, Langley Porter unhesitatingly would answer: "Young men. Give your developing and enthusiastic young minds an opportunity, and all else will be added unto you."

Probably the outstanding characteristic of Langley Porter is that quality of head and heart—his love for his fellow man. May this modern Abou Ben Adhem yet live years on end further to enrich the lives of them about him.

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ELECTROENCEPHALOGRAPHY IN CEREBRAL PALSY

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THE study of cerebral palsy has gained great impetus as a result of public interest and the development of specific research projects in this field. One of the more interesting developments in this work has been the application of electroencephalography to the problem. Electroencephalography, in that it affords data on cerebral physiology, is of considerable potential value in those conditions associated with cerebral pathology and abnormal physiology. This is especially true in those cerebral palsy patients whose condition is complicated by convulsive disorders.

Only two studies in this field have come to our attention. Perlstein, Gibbs, and Gibbs[1] studied 212 spastic children under 16 years of age by electroencephalography and found this technique had considerable diagnostic and prognostic value in cerebral palsy. A more limited study has been reported by Ross, Norfleet, and Löwenbach,[2] which questions the value of electroencephalography in cerebral palsy.

In the course of a local project on cerebral palsy we have had occasion to obtain electroencephalograms on 187 patients. Inasmuch as our studies have been directed at assessing the location and degree of cerebral pathology, as well as observing seizure discharge, a report of our results has seemed justified. Our object has been to evaluate the use of electroencephalography as a diagnostic tool in cerebral palsy.

MATERIALS AND METHODS

The study is based upon 187 children with cerebral palsy, from 1 to 21 years of age, who received adequate clinical, psychometric, and electroencephalographic studies in the Cerebral Palsy Diagnostic and Treatment Center of the University of California Hospital*

The group consisted of 128 spastics, 53 athetoids, and 6 others (ataxics and undetermined types). The latter have been omitted from several of the analyses presented in this study, inasmuch as the number of ataxics were too few to be of statistical significance.

Clinical Studies.—Histories were carefully obtained in an attempt to determine the etiology and course of the condition in each case. In assessing the etiological factors of cerebral palsy, the difficulty of differentiating between congenital defects, birth injuries, and anoxemia must be kept in mind. It is obvious that the child who has a congenital maldevelopment of the brain may act in such

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*In cooperation with the California State Department of Education and the California State Department of Public Health.

a disturbed fashion at birth that his condition may be mistaken for a birth injury, or again respiratory embarrassment, on the same basis, may be confused with anoxia.

Complete physical and neurological examinations were carried out on all patients.

A psychometric test was performed in all instances to assess the mental ability of the children. Repeat psychometric studies were obtained in many instances when the validity of the initial test was doubtful.

Laboratory Studies.—X-rays of the skull were obtained in all cases and other laboratory tests were made as indicated in each case.

Electroencephalographic Studies.—The same methods of analysis and techniques of recording have been adhered to in the present study as were presented in a previous paper.[3] In the great majority of cerebral palsy cases, a 12-electrode placement was employed with both scalp-to-ear and scalp-to-scalp recording. In addition to the usual methods of analysis, a systematic comparison of the differences in the hemispheric synchrony, form, frequency, and potential of many homologous tracings were obtained simultaneously, inasmuch as we have found that this additional data is of considerable value for purposes of localization in conditions such as cerebral palsy where focal pathology is suspected.

Statistical Method of Analysis.—The pertinent findings by each method of study were recorded on punch cards* in accordance with a prearranged plan of significant categories. This permitted a rapid review of any desired category and facilitated the type of correlative analysis required in the study.

TABLE I. EEG FINDINGS IN CEREBRAL PALSY*

CLINICAL TYPE	NO. OF CASES	EEG CLASSIFICATION			
		NORMAL PER CENT	BORDERLINE PER CENT	ABNORMAL	
				TOTAL PER CENT	FOCAL PER CENT
Spastics	128	13	2	85	62
Athetoids	53	32	8	60	32

*Excluding 4 ataxics and 2 unclassified.

RESULTS

The electroencephalographic findings (normal, borderline, abnormal, and those showing focal changes) were correlated with the two principal types of cerebral palsy (spastics and athetoids) in Table I. In confirmation of the findings of Perlstein, Gibbs, and Gibbs,[1] electroencephalographic abnormality occurred to a considerably greater extent in the spastic group (85 per cent) than in the athetoid group (60 per cent). Again, electroencephalographic evidence suggestive of focal pathology was noted in approximately 62 per cent of spastics and only 32 per cent of athetoids. Correspondingly, although normal electroencephalograms were obtained in only 1 out of 8 of the spastic group, they were found in approximately 1 out of 3 of the athetoid group.

Correlation of the electroencephalographic findings with "known" etiology (Table II), showed abnormal electroencephalograms in nearly 98 per cent of spastics with a history of injury or infection (67 per cent of corresponding group

*E-Z Sort System, Ltd., 45 Second St., San Francisco, Calif.

of athetoids) and focal findings in 75 per cent of the same spastic group (45 per cent of corresponding athetoid group). Approximately 80 per cent of spasties of anoxemic, congenital, and premature origin showed abnormal electroencephalograms. Of special interest was the fact that an Rh etiology was found alone in the athetoid group and was associated with abnormal electroencephalograms in 5 out of 8 patients, 3 of whom showed findings suggestive of focal pathology.

TABLE II. EEG FINDINGS IN SPASTIC AND ATHETOID TYPES OF CEREBRAL PALSY ACCORDING TO THEIR KNOWN ETIOLOGY*

KNOWN ETIOLOGICAL FACTORS	NO. OF CASES		EEG CLASSIFICATION							
			NORMAL		BORDERLINE		ABNORMAL			
							TOTAL		FOCAL	
	SP.	ATH.	SP. %	ATH. %	SP. %	ATH. %	SP. %	ATH. %	SP. %	ATH. %
Injury and infection†	44	9	0	33	2	0	98	67	75	45
Anoxia, congenital, and premature‡	40	18	17	17	0	11	83	72	65	33
Rh	0	8	0	25	0	12	0	63	0	38

*Excluding all cases of doubtful or unknown etiology.

†The EEG findings in cerebral palsy due to injury were not sufficiently different from those due to infection to warrant their separate consideration.

‡The EEG findings in cerebral palsy due to anoxia were not sufficiently different from those due to congenital causes or prematurity to warrant their separate consideration.

The severity of cerebral palsy was graded in three categories: mild, moderate, and severe. In the spastic group, 40 per cent had mild involvement; 40 per cent moderate, and 20 per cent, severe. In the athetoid group, 37 per cent showed mild involvement; 26 per cent, moderate, and 37 per cent, severe involvement. A striking and consistent difference was found between spastics and athetoids for all degrees of clinical involvement (Table III). Depending upon the severity of involvement, the spastic group showed from 12 to 52 per cent more abnormal electroencephalograms than the athetoid group. Correspondingly, focal changes were observed 25 per cent more commonly in the spastic group than in the athetoid group.

TABLE III. EEG FINDINGS IN SPASTIC AND ATHETOID TYPES OF CEREBRAL PALSY ACCORDING TO THE KNOWN SEVERITY OF CLINICAL INVOLVEMENT*

SEVERITY OF CLINICAL INVOLVEMENT	NO. OF CASES		EEG CLASSIFICATION							
			NORMAL		BORDERLINE		ABNORMAL			
							TOTAL		FOCAL	
	SP.	ATH.	SP. %	ATH. %	SP. %	ATH. %	SP. %	ATH. %	SP. %	ATH. %
Mild	42	21	17	28	5	5	78	67	57	24
Moderate	40	10	8	40	0	20	92	40	68	40
Severe										

*Excluding all cases of doubtful or undetermined severity.

Psychometric studies were graded according to the usual categories of superior, normal, borderline, moron, imbecile, and idiot. No significant difference appeared in this respect between the spastic and athetoid groups. Superior, normal, and borderline intelligence quotients were found in approximately one-half of each group and about one-fourth of each group fell in the moron and also in the combined imbecile-idiot categories. Correspondingly, no definite cor-

relation could be established between the electroencephalographic findings and intelligence quotients. Nevertheless, it was of some interest that while in the spastic group 8 out of 9 normal electroencephalograms were correlated with a superior or normal intelligence quotient, only 37 out of 61 abnormal electroencephalograms were on patients with a normal intelligence quotient or better.

Of the spastic group, 65 per cent gave a history of convulsions and 35 per cent of the athetoid group had convulsions. The incidence of abnormal electroencephalograms was higher among spastics subject to convulsions (88 per cent) than among athetoids subject to convulsions (61 per cent) (Table IV). Correspondingly, 64 per cent of convulsive spastics and 28 per cent of convulsive athetoids showed focal electroencephalograms.

TABLE IV. EEG FINDINGS IN CEREBRAL PALSY COMPLICATED BY CONVULSIVE DISORDERS

CLINICAL TYPES	NO. OF CASES	EEG CLASSIFICATIONS			
		NORMAL %	BORDERLINE %	ABNORMAL TOTAL %	ABNORMAL FOCAL %
Spastic	83	8	4	88	64
Athetoid	18	33	6	61	28

Fifty-five per cent of spastics in whom the type of convulsion was known were subject to grand mal, 23 per cent to Jacksonian seizures, and 22 per cent to petit mal. The corresponding figures for the athetoid group with known types of convulsions were: 64 per cent had grand mal, none had Jacksonian seizures, and 36 per cent had petit mal. Whereas over 90 per cent of spastics with grand mal or Jacksonian convulsive states showed abnormal electroencephalograms (and approximately 75 per cent showed focal electroencephalograms), only 50 per cent of the spastics with petit mal showed either abnormal or focal electroencephalograms.

Eighty-nine per cent of the spastic group were known to have severe convulsions and in this group 97 per cent were found to have abnormal electroencephalograms and 90 per cent showed focal changes. Although the number of cases with mild convulsions are insufficient to permit comparison, the percentages quoted for severe spastics are significantly higher than the corresponding figures for the spastic group with convulsions in general, that is, without respect to the severity of their spells.

It has been a common clinical observation that the handedness of patients, who have sustained cerebral pathological changes early in life, is almost universally associated with the least involved cerebral hemisphere, regardless of inherent dominance. This was confirmed in the present study. In patients whose handedness was well established and who also had suffered definite cerebral injury as judged by their neurological localizing findings, the handedness of 48 out of 50 (96 per cent) was associated with the hemisphere of least involvement. This was also borne out by electroencephalography which showed focal changes over the cerebrum controlling the opposite side from the handedness of the patient in 91 per cent. In those patients of this group, who showed both neurological localization and focal changes by electroencephalography, the

electroencephalographic localization correlated with the clinical findings in nearly 98 per cent of instances.

DISCUSSION

The attempts which have been made to utilize electroencephalography as a diagnostic and prognostic procedure in cerebral palsy have varied widely in their conclusions. Whereas, Perlstein, Gibbs, and Gibbs[1] stress the value of electroencephalography in cerebral palsy and particularly so in cerebral palsy associated with seizures, Ross, Norfleet, and Löwenbach,[2] in a more limited study, question the value of electroencephalography in this condition.

The value of the electroencephalogram in differentiating between the two main clinical types of cerebral palsy would appear to be questionable. Although it is true that there is a greater incidence of abnormal electroencephalograms among the spastics than the athetoids, the percentage difference is not sufficient to warrant using this procedure for purposes of differential diagnosis. Furthermore, abnormal electroencephalograms appear sufficiently common in the athetoid group to make it impossible to rule this condition out of consideration in any given case. In cerebral palsy, therefore, it would appear to us that the clinical classification must still be determined by clinical methods and that the value of electroencephalography for purposes of differential diagnosis is largely limited to that small group of patients in whom the clinical differentiation is difficult.

A review of our data along the lines of analysis followed by Perlstein, Gibbs, and Gibbs[1] showed results which were qualitatively analogous to theirs. In several instances, however, our findings were less striking from a quantitative standpoint than those of the authors quoted, so that the statistical value of our results for purposes of differential diagnosis and prognosis appear less valid. For example, Perlstein, Gibbs, and Gibbs conclude that "A history of seizures weights the evidence in favor of the case being a spastic 68 per cent (86 of a total of 142) to 17 per cent (12 of a total of 70) or four to one, regardless of the electroencephalographic findings." Our own data showed that 85 of a total of 128 spastics (66.4 per cent) and 18 of a total of 53 athetoids (34 per cent) had a history of convulsions, giving a ratio of about two to one as opposed to the ratio of four to one found by Perlstein, Gibbs, and Gibbs.

On the other hand, our results confirm the conclusion of Perlstein, Gibbs, and Gibbs that "if there has been no history of seizures, the finding of a normal electroencephalogram gives some assurance that clinically evident seizures will not occur, the chances being approximately eight to one (89 per cent to 11 per cent) in favor of their non-appearance." Twenty of a total of 187 patients (10.7 per cent) in our series had no history of seizures and also showed normal electroencephalograms.

It is our belief, however, that the wide divergence of opinion as to the prognostic value of electroencephalography with regard to the probable incidence of seizures at a later date in those patients who initially show an electroencephalogram suggestive of seizure discharge, but without a history of clinical spells, cannot be settled by the data presented in either of the previous studies on this

subject [1,2] or our own. A prolonged clinical follow-up in a large series of cerebral palsy patients, in whom serial electroencephalograms in addition to the initial test would be desirable, can alone afford the facts necessary to determine this point. The degree of discrepancy between the electroencephalogram and clinical findings in this respect and the frequent tendency for improvement with growth, in both the electroencephalogram and the convulsive susceptibility of children, by no means make it clear that one can safely prognosticate seizures in a child on the basis of electroencephalographic findings alone.

The poor correlation between the electroencephalographic findings and the intelligence of the patients noted in this study confirms the observation of Ross, Norfleet, and Löwenbach[2] and is not surprising in view of other studies (Kreezer[4] and Lindsley[5]) along this line.

SUMMARY

In summary it is obvious that the neurological and mental disability in each individual case of cerebral palsy can best be evaluated by clinical methods (physical, neurological, and psychometric studies). The value of electroencephalography in these all-important aspects of cerebral palsy is of a limited and secondary character. As a laboratory procedure, electroencephalography always should be correlated with and subserve the clinical studies which are of primary importance in this condition. When properly used, however, electroencephalography can be of considerable assistance in cerebral palsy. Its value and limitations in the diagnosis and prognosis of convulsive reactivity and in the localization of cerebral pathology is essentially the same in cerebral palsy as in other neurological disorders. In the majority of cases, its value will be of a confirmatory nature and serve to fill out the picture of the condition under study from a physiologic standpoint. In occasional instances, where physiologic factors are paramount, or the relationship between focal pathology and epileptic foci is of considerable significance to one's understanding of the clinical problem involved, electroencephalography assumes major importance. Our experience with electroencephalography in cerebral palsy leads us to believe that there is no more reason to belittle the value of electroencephalography in this condition than in any other neurological disorder, which is associated in a high percentage of cases with cerebral pathology and dysfunction, including convulsive reactivity. On the other hand, electroencephalography possesses no unique diagnostic or prognostic potentialities in cerebral palsy over and above that which electroencephalography possesses in several other neurological conditions.

CONCLUSION

An electroencephalographic study of 187 children with cerebral palsy indicates that electroencephalography possesses essentially the same diagnostic and prognostic value in this condition as it has been found to possess in other neurological disorders associated in a high percentage of cases with cerebral pathology and dysfunction, including convulsive reactivity. Claims, which either belittle its value in this condition or, on the other hand, stress its unique diagnostic potentialities in cerebral palsy, would appear to be unwarranted.

The authors wish to express their appreciation to Marisa Lusiardo de Leon for her invaluable technical assistance.

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THE EFFECT OF TRANSFUSIONS AND ANTIBIOTICS UPON THE DURATION OF LIFE IN CHILDREN WITH LYMPHOGENOUS LEUCEMIA

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RECENT interest in chemotherapy for leucemia in children has emphasized the need for basic data on the natural history of the disease. None of the therapeutic procedures thus far available change the ultimate final prognosis. On the other hand, temporary hematological and general clinical improvements are achieved in approximately one-third of the patients with the use of folic acid antagonists, and present results suggest that temporary ameliorative effects are also obtained with adrenocorticotrophic hormone and 17-hydroxy-11-dehydrocorticosterone. The clinical impression is that these transient improvements are reflected in prolongation of life in children with leucemia, although no conclusive information on this point exists in the literature. Moreover, the available data do not take into adequate consideration the fact that during the past decade blood transfusions, antibiotics, and other supportive measures have had an increasingly important role in the management of childhood leucemia. Since hemorrhage and intercurrent infection have been the two major immediate causes of death in leucemia in children, it is conceivable that some of the effects attributed to chemotherapeutic agents are at least in part due to supportive measures.

This report deals with the duration of life in children with lymphogenous leucemia, and the influence of transfusions and of penicillin and/or sulfonamides upon the course of the disease.

MATERIALS AND METHODS

A review was made of consecutive cases of leucemia in children under 15 years of age who were admitted to the Pediatrics Service of the University of California Hospital during the period 1939 to 1948, inclusive.

There were 103 cases of leucemia, of which 90 were classified as lymphogenous, 10 myelogenous, and 3 monocytic in type (Fig. 1). Because of its prevalence in children, only the cases with lymphogenous leucemia were studied.

Follow-up data were not available on 9 patients, and, for the statistical evaluation of survival, 5 additional patients were excluded, leaving a total of 76 cases. The five cases which were excluded from the analysis included the following: An accidental death due to puncture of a thymic blood vessel during a sternal marrow aspiration occurred in one child, four months after apparent

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onset of the disease; this patient had received no treatment. One patient had a Blalock operation for a congenital cardiac anomaly, and developed a leucemic blood picture eleven months later; she received no treatment and died one month later. The third patient was excluded because of the presence of an arteriovenous aneurysm prior to the onset of leucemia. Two cases were excluded from the statistical analysis because of long survival which resulted in skewed distribution of the data. One of these patients was alive five years after the apparent onset of the disease. The other one died eighty-four months after the onset of lymphogenous leucemia as diagnosed repeatedly on the basis of clinical and hematological criteria including bone marrow aspirations; however, the final clinical diagnosis was aplastic anemia and necropsy was not performed. Both patients received blood transfusions and antibiotics. The exclusion of these five cases does not alter the conclusions of this report and, in fact, their inclusion would further accentuate the differences in survival elicited by the present analysis.

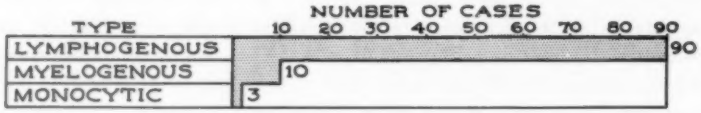

Fig. 1.—Types of leucemia in 103 children admitted to the University of California Hospital, 1939 to 1948.

The duration of disease was determined from the time of appearance of the first major signs and symptoms to the time of death. The onset of leucemia is usually insidious and admittedly difficult to determine exactly. It was recorded as accurately as possible, however. Clinical manifestations attributable to subsequently established diagnosis of lymphogenous leucemia included marked lymphadenopathy, progressive severe anemia, hemorrhagic diathesis, severe bone and joint pain, and enlargement of the liver and spleen. The diagnosis of leucemia was made by the usual clinical and hematological criteria, including in each case an examination of the bone marrow.

The cases were divided into four groups: (1) Eighteen cases received no treatment with irradiation, blood transfusions, penicillin, or sulfonamides; (2) patients who received irradiation treatment, either by x-ray or radiophosphorus. Most of this group of 17 cases also received blood transfusions and penicillin or sulfonamides at some time during the course of the disease; (3) 24 cases received blood transfusions during their illness, but no antibiotics; (4) patients who were treated with both blood transfusions and penicillin and/or sulfonamides. Penicillin was given intramuscularly for periods up to thirty days although in most instances it was discontinued within one week. Sulfonamides were given orally in usual doses for periods not exceeding two weeks. There was a total of 17 cases in this category.

Iron, vitamins, and liver preparations were administered to many of the patients in all four groups, but exact data sufficient for proper evaluation were not available.

RESULTS

Of all 90 cases of lymphogenous leucemia, 56 were males and 34 were females. Peaks in incidence occurred at the age of 2 and of 4 years, with a range from 3 months to 14 years (Fig. 2). The average age at onset was 5.0 years. The duration of survival in patients of different ages at onset is given in Fig. 3. Statistical analysis of these data show a slight, but not statistically significant, tendency for duration of survival to increase with age at onset.

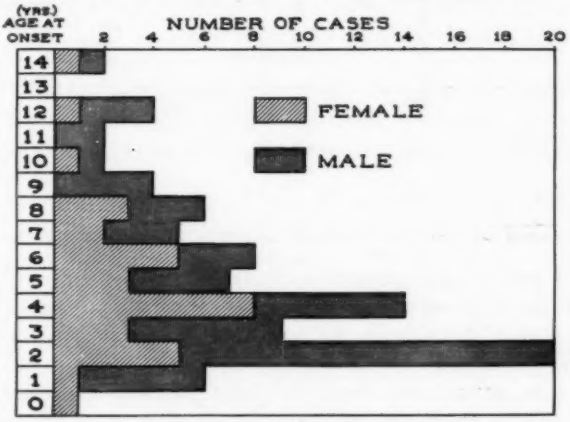

Fig. 2.—Age at which 90 children first exhibited major symptoms of lymphogenous leucemia.

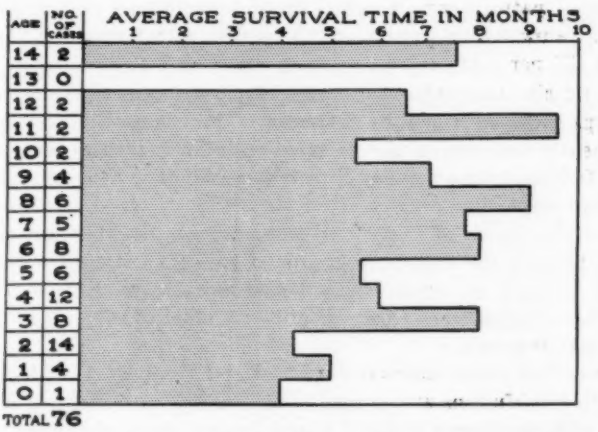

Fig. 3.—Average duration of survival of 76 children with lymphogenous leucemia, according to age at onset.

The duration of survival was obtained in 76 patients (Table I).

The average time of survival of 18 cases who received no treatment was 5.6 months, with a range of 2 to 16 months. Three cases (17 per cent) lived beyond 9 months.

TABLE I. DURATION OF SURVIVAL OF 76 CHILDREN WITH LYMPHOGENOUS LEUCEMIA

SURVIVAL TIME (MONTHS)	THERAPY			
	NO TREATMENT	X-RAY	BLOOD ONLY	BLOOD AND PENICILLIN AND/OR SULFONAMIDES
Over 16	0	0	0	1
15-16	2	0	0	0
13-14	0	0	0	2
11-12	0	2	0	2
9-10	1	2	6	4
7-8	2	2	5	2
5-6	2	2	6	3
3-4	7	9	5	3
1-2	4	0	2	0
Total	18.0	17.0	24.0	17.0
Average*	5.6	5.8	6.0	8.9
Standard Deviation*	4.0	2.7	2.4	4.8
Standard Error of Mean*	0.9	0.6	0.5	1.2
Mean Age at Onset (years)	4.4	6.2	5.0	4.6

*Values obtained from raw data and not from data as grouped in Table.

Seventeen patients who received x-ray treatment and supportive therapy of blood and antibiotics at some time during the course of the disease had an average survival time of 5.8 months, with a range from 3 to 11 months. Four of these patients (23 per cent) lived beyond 9 months.

Twenty-four patients who received blood transfusions, at some time during their illness, but no antibiotics, survived for an average of 6.0 months, with a range of 2 to 9 months. Six cases (25 per cent) survived 9 months or longer.

Seventeen patients who received blood transfusions and penicillin and/or sulfonamides survived an average of 8.9 months, with a range of 3 to 23 months. Nine cases (53 per cent) in this category survived 9 to 23 months.

It should also be emphasized that 17 to 25 per cent of the cases in the first three groups survived 9 months or longer. This makes it clear that claims for any therapeutic measures cannot be based on individual cases because of the considerable likelihood that these individuals would have had long survival times even without supportive therapy.

Statistical analysis of these four groups shows that there are no significant differences between the first three groups of patients. It may be concluded that irradiation therapy, or treatment by transfusions alone, have not been demonstrated to have a significant effect upon the duration of survival in children with lymphogenous leucemia.

However, the mean survival period of the group of 17 patients who were treated with transfusions and penicillin and/or sulfonamides was 8.9 months, as compared with the means of 5.6, 5.8, and 6.0 months in the other three groups. This mean survival time is significantly greater ($P = 0.03$) than the mean survival time of patients in any of the other three groups. Two cases of long survival, one of whom died at 84 months and the other alive sixty months after apparent onset, were excluded from the analysis. Both of these patients were treated with transfusions and antibiotics. If these two cases were included, the difference between the group treated with antibiotics and transfusions and all

other groups would be even more significant. Furthermore, the average age at which onset of the disease was noted in the group is slightly lower than the average for the other three groups (4.6 years vs. 5.2 years) and, hence, age cannot be considered as a contributing factor in the increased survival times of the patients treated with transfusions and antibiotics (Figs. 2 and 3). It may be concluded with a reasonable degree of certainty that the addition of penicillin and sulfonamides and transfusions to the treatment of children with lymphogenous leucemia was associated with an increased time of survival in this series.

DISCUSSION

Chronic leucemias are rare in children.[1] Occasional reports of chronic myelogenous leucemia in children have appeared, Steinbrink,[2] Malmberg,[3] Esp,[4] but only a few cases of chronic lymphogenous leucemia in this age group have ever been authenticated.[5-9]

The designation of an acute or chronic leucemia is retrospective and dependent in part upon the severity and the duration of the illness. Many cases exhibit a subacute course intermediate between that of acute or chronic leucemia. In order to avoid a controversy, insoluble at present, the simple designation of lymphogenous leucemia in children was employed.

The literature on leucemia in childhood contains several extensive series with data on the incidence, sex distribution, and duration of illness. Cooke,[6] Booth and Rembolt,[10] Falkenstein and Fowler,[11] Sullivan, Rice, and Cassidy,[12] and Dale[13] summarized data on 282 patients under 14 years of age with leucemia, of which 62 per cent were males. The average duration of survival in 252 cases, as measured from the onset of symptoms, was from 3.6 to 5.5 months. The results of Dale[13] on 38 cases are in almost exact agreement with the presently reported data on children who were not treated, or were treated with transfusions or irradiation. The data combine lymphogenous and myelogenous leucemia (Table II).

TABLE II. DURATION OF SURVIVAL IN CHILDREN WITH LEUCEMIA

AUTHOR	SOURCE OF DATA	DATES	DURATION		
			CASES (NO.)	SPREAD (MONTHS)	AVERAGE (MONTHS)
Cooke[6]	Missouri	1918-1933	50	0.5-9	3.6
Booth and Rembolt[10]	Minnesota	1930-1938	40	0.1-7	4.2
Falkenstein and Fowler[11]	Iowa	to 1943	61	0.5-14	4.3
Sullivan et al[12]	Dist. Columbia	1938-1947	63	0.5-15	4.0
Dale[13]	New York	1932-1948	38*	0.5-20	5.5

*Excluding 1 case of 34 months' duration.

There is but scanty information in the literature regarding the influence of supportive treatment on the course of childhood leucemia and on the length of survival. Most hematologists have seen at least a few instances of transient beneficial effect of blood transfusions on children with acute lymphatic leucemia. Schwind[14] observed that infusion of blood plasma was followed by a decrease in the percentage of myeloblasts in the blood. Dreyfus[15] has stated that the probability of a remission is related to the number of blood transfusions and the total

amount of blood infused. Replacement transfusions have also been followed by remissions.[16, 17] On the other hand, Cooke[6] concluded that the effect of transfusions is transient and of questionable value. Falkenstein and Fowler[11] similarly reported that transfusions were given to thirty-four patients, and an analysis of the data revealed no evidence that the administration of blood prolonged the life of the patients. Sullivan and collaborators[12] stated that blood transfusion is the only measure that prolongs life appreciably, but gave no statistical data to support this contention.

The present data agree with the conclusions of Cooke[6] and of Falkenstein and Fowler[11] in that the group of children who received treatment with irradiation or with blood transfusions alone survived no longer than patients who received no treatment. It must be realized, however, that the transfusions were given intermittently and not in massive amounts.

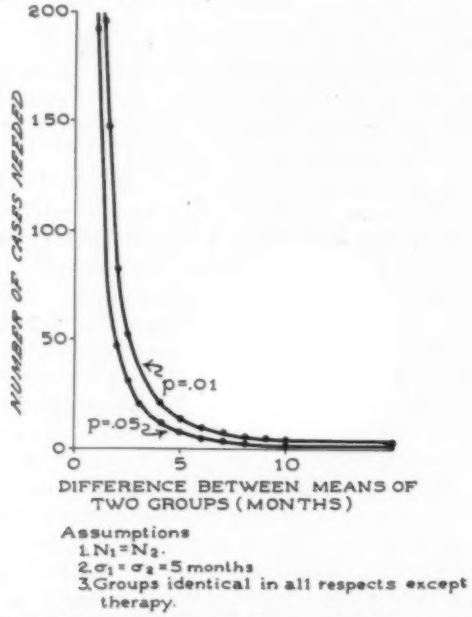

Fig. 4.—Number of cases needed to demonstrate differences between two therapeutic methods in the treatment of children with lymphogenous leucemia with 50 per cent certainty.

In contrast, patients who received treatment with penicillin and/or sulfonamides and with repeated transfusions showed a significant prolongation of life. From these data alone it is of course not possible to determine whether this increase in survival time is the result of some specific actions of the antibiotics and blood transfusions against the leucemic manifestations or whether such therapy exerts its effects merely by improving the general condition of the patient and by controlling intercurrent infections.

The employment of penicillin, sulfonamides, and other antibiotic agents have aborted and controlled many infections which frequently have been the

terminating event in patients with an acute leucemia. In addition, there have been reports of the coagulant property of the antibiotics,[18] but they lack confirmation.[19] If the antibiotics indeed diminish the hemorrhagic tendency in patients with acute leucemia, it would indicate a possible favorable effect of these agents in this group of diseases other than of a purely antibacterial nature. One must also consider the chemotherapeutic effect of antibiotic agents on as yet undiscovered infectious agents possibly related etiologically to leucemia.[7]

Statistical analysis of final results on sufficient numbers of adequately controlled cases is the only method by which prolongation of life or other effects of therapy can be acceptably substantiated. This involves comparison of groups of treated patients with similar groups of "untreated controls," or at least with groups treated by some other method but similar in regard to sex, age, stage of disease, and general condition. The presently reported groups of children with leucemia appear to fulfill the requirement of coming from the same population. The data also allow statistical estimations of the number of cases which would be needed in order to demonstrate differences between the effects of various forms of treatment in childhood leucemia. These calculations are given in Fig. 4. Assuming that the untreated control group of another investigation shows the same mean survival and standard deviation, thirty-seven cases which are treated by a particular agent and survive on the average three months longer are necessary for a conclusion that is statistically significant at the 1 per cent level ($P = 0.01$), 50 per cent of the time. To be more certain of attaining results significant at the 1 per cent level, a larger number of cases would be needed. For example, for 95 per cent certainty at the 1 per cent level with a difference of three months between the means of the two groups, the number of cases needed in control and experimental groups rises to 100. The statistical method, therefore, is not only essential in the final evaluation of the data but is as necessary in the formulation of an experimental study in which conclusive results are desired.

Evaluation of the treatment of leucemia in children requires an adequate control series of cases. In clinical therapeutic investigations, it is usual to give supportive therapy rather than to withhold treatment of any kind. Therefore, the effects of such therapy must be considered. Heretofore, such supportive therapy has been considered to have relatively little or no effect on duration of survival.

That some folic acid antagonists and other agents produce marked hematological changes in many patients with acute leucemia cannot be denied.[20-22] Clinical investigations with these agents have proceeded to the point where prolongation of life may be used to evaluate their efficacy. The influence of blood transfusions, antibiotics, and antihemorrhagic agents in the clinical management of children with leucemia who also receive such new agents must be considered before the chemical agents alone can be held responsible for the prolongation of life.

SUMMARY

1. Ninety cases of lymphogenous leucemia in children under 14 years of age were studied, of which 76 were analyzed relative to duration of survival.

2. The average duration of survival of 18 cases of untreated lymphogenous leucemia in children was 5.6 months.

3. A group of 17 children who were treated with irradiation (x-ray or radiophosphorus) plus blood transfusions and antibiotics survived 5.8 months.

4. Twenty-four patients received blood transfusions but no penicillin or sulfonamide therapy and survived an average of 6.0 months.

5. Seventeen patients who received blood transfusions and antibiotics survived an average of 8.9 months, a significantly prolonged survival time in comparison with the first three groups.

6. The necessity of statistical comparison of patients treated experimentally by chemotherapeutic agents with an adequately controlled comparable group is emphasized.

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SIGNS AND SYMPTOMS OF SUPRATENTORIAL BRAIN TUMORS IN CHILDHOOD

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IN THE literature concerning tumors of the brain in childhood, there are many studies of neoplasms in the posterior fossa, but those arising above the tentorium have received much less attention. This has resulted in the misconception that tumors in this region are rare in childhood and has led to later and less accurate diagnosis of these lesions, despite their comparative frequency and relatively better prognosis.

We have had recent occasion to review the brain tumors which have been found in children treated at the University of California Hospital on the Pediatric and Neurosurgical Services since 1914. Of the 220 tumors found in children during this period, 96, or 44 per cent, have been located above the tentorium. This incidence, which is higher than has been noted in any previous study that has come to our attention, has led us to the conclusion that signs and symptoms of tumors in this area merit thought and consideration greater than has heretofore been extended them.

Brain tumors in childhood are classified by the same criteria as are applied to brain tumors generally. The term includes not only tumors of the glial and neuronal series, but also tumors of the meninges, of the central nervous system or cranial nerves, of the intracranial endocrine glands, of blood vessels, and of adjacent cranial structures. In this series, the most frequently encountered tumor was angioma which was present in twelve patients. Its predominance may be attributed to the recent interest in vascular diseases attending the development of cerebral angiography. Next in frequency, occurring in ten cases, was Rathke pouch "cyst," with pinealoma and astrocytoma (seven of each) sharing third position in incidence. Meningiomas, dermoid cysts, and glioblastoma multiforme constitute the next group, followed by unclassified gliomas and polar spongioblastomas. The remainder of the series is composed of papilloma of the choroid plexus, neuroblastoma, hemangioendothelioma, metastatic carcinoma, ependymoma, neurofibroma, and oligodendroglioma.

The signs and symptoms presented by these various growths obviously are in some degree related to the character and therefore the location of the growth, and the incidence of any finding is likewise related to the frequency with which particular tumors, especially those about the base of the brain, are encountered. Comments, though, concerning the signs and symptoms will be based on the supratentorial group as a whole and particular allusion to tumor

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types will be omitted. Here, as in the adult, all tumors growing within the cranium are, by their very location, potentially fatal, and the essential factor, we believe, is the identification of a growth, its location and pathological characteristics being of secondary significance.

The importance of early diagnosis of neoplasm generally has been emphasized and re-emphasized, and in this essential factor, supratentorial tumors in childhood are no exception. Probably because of the great emphasis on posterior fossa tumors in childhood, the supratentorial group seems to have received proportionately less attention, which has led to delays in appreciation of the presence of a tumor. One of the reasons for failing to think of tumor above the tentorium is, we believe, the matter already mentioned, the failure to recognize the frequency with which these growths may be found in childhood. That tumors of the posterior fossa are more frequently sought out seems apparent from the evidence at hand.

In our series, somewhat less than 50 per cent of the tumors were suspected prior to the child's hospitalization for study. Yet 37 per cent of all patients had had symptoms for more than a year which, in the bright light of retrospect, were clearly referable to the lesions found. The cause of the delay, in addition to the point of incidence mentioned, was to a large degree similar to that causing delay in recognition of brain tumors generally. Rand and van Wagenen[1] have pointed to the frequency with which fundus examinations are omitted and x-ray studies delayed. Redlich, Rembrandt, and Brody,[2] in analyzing their cases, were impressed by such frequent early diagnoses as "nothing wrong," "neuropsychiatric or emotional disturbance," "convulsive state," "vascular accident." Among the diagnoses that were erroneously suggested in this series have been gastrointestinal upset, encephalitis, post-traumatic state, degenerative disease of the nervous system, and the currently fashionable "behavior disturbance."

Exacerbations and remissions of signs and symptoms have frequently been misleading. As has already been noted by Bailey[3] and others, clinical swings in symptoms and signs must not be considered as strong evidence against the existence of a brain tumor during childhood.

Age also cannot justify the failure to consider brain tumor in differential diagnosis. In this series, the youngest patient was a 3-day-old infant who had an angioma of the choroid plexus. (The case is being reported elsewhere.) Supratentorial tumors have been found at all ages, though an increased incidence has been noted at the ages of 3 to 6 years and at 13 to 14 years, these peaks being extremely prominent in female patients.

The most frequent symptom of supratentorial tumors in childhood is headache. The frequency of this symptom, both as a chief complaint and as an initial symptom, has been striking in our records. Putnam[4] has already made the point that while headache is less frequent in childhood than in adult life, it is more likely to be of serious consequence. It was present in 58 per cent of the patients with supratentorial lesions. In this group of patients we were able to get no help at all from the location of the headache which was usually generalized, and if localized was valuable in only two instances as a clue to the location of the lesion.

Vomiting was second in frequency as a symptom of supratentorial tumor, and was present as a manifestation of the disease in 46 per cent of these patients. It is of interest that the vomiting was projectile in only one case in ten in which this symptom was present. Projectile vomiting was almost entirely confined to the lower age groups.

Evidence of loss of vision was present in 31 per cent of patients. Generalized visual loss was a late manifestation of increased intracranial pressure. It was associated with changes in the optic discs, either due to primary atrophy or related to papilledema. Localized visual loss due to direct pressure on the optic nerves was seen with the parasellar or intrasellar invasion of some of the angiomas. Unilateral loss of vision from direct involvement of the vessels to the eye as part of an angiomatous process was seen, and intracranial hemorrhage, as in angiomas, also played a role in this symptom. Double vision was present in 22 per cent of the patients, most of whom were children with tumors about the sella turcica. It was as frequent an initial symptom as a chief complaint. Usually in patients with double vision there was manifest failure of parallelism in the extraocular movements.

Convulsive seizures were present in 30 per cent of the patients and 50 per cent of such seizures were focal. Focal convulsive manifestations do not have nearly the significance in the child that they have in adults, but the unexplained appearance of focal or Jacksonian convulsions in the child can never be allowed to pass unnoticed. In a goodly number of these patients, it was the initial symptom relating to the tumor.

Ataxia, noted in 24 per cent of the patients, was manifest in both the trunk and in the extremities; the side affected was equally divided. It was more often an initial symptom than a chief complaint. At times what was described and interpreted by the parents as clumsiness proved to be not lack of coordination, but rather evidence of weakness. In the young child this fine point of differentiation is often extremely difficult to make.

In 5 per cent of the patients the presenting symptoms were those more commonly associated with craniospinal infection. Occurring at a time when meningitis and encephalitis are commonly found in children, considerable confusion has usually attended the differential consideration of such symptoms as stiffness of the neck, low grade fever, and even increased cell count and protein in the cerebrospinal fluid. Nearly all tumors in the brain may seed to the subarachnoid space. Circumstances permitting this seeding often permit irritation of the meninges with the resulting syndrome resembling infection of the central nervous system. Rarely tumor cells may be identified in the spinal fluid; more commonly the true source of the symptom is revealed during the subsequent course of the disease or by other methods of investigation.

All too often, as revealed in this series of patients, the signs of supratentorial tumor are the late signs of an intracranial, space-occupying mass. In 55 per cent of these patients papilledema was present, often with associated visual loss. There is a common misconception that it is possible to differentiate a supratentorial tumor from one in the posterior fossa by the general appearance of the papilledema, its degree, the presence and extent of

hemorrhage, vessel engorgement, etc. The observations made in this group of patients do not permit corroboration of this impression. Furthermore, the papilledema was usually present bilaterally and apparently was not affected to a major degree by direct compression of a tumor immediately supra-adjacent to the nerve on one side (Foster Kennedy's syndrome).

Obvious weakness of the extermities was noted in 35 per cent of the patients. Usually it was unilateral, and the right and left sides were equally represented. In only four patients with supratentorial tumors was there bilateral weakness of the extremities. As previously noted, weakness was often interpreted by the parents as being clumsiness and was sometimes difficult to differentiate from ataxia. Frank ataxia was localized to one side or the other in all but nine cases. In some of the patients the ataxia took on the appearance of so-called body ataxia.

Increase in head size or distortion of the cranial configuration was present in 25 per cent of the patients, chiefly in the younger age groups. In the same group and to almost the same percentage was found the so-called "cracked pot" percussion note (McEwen's sign). These two signs appear as manifestations of increased intracranial pressure up to the time of closing of the sutures.

We were surprised to find nystagmus present in 15 per cent of the patients. Lateral nystagmus and vertical nystagmus were occasionally mentioned in the descriptions. Ocular nystagmus related to diminished visual acuity was not included in this series as a sign of supratentorial tumor.

An intracranial bruit was heard in eight supratentorial tumors and only six of these proved subsequently to be angiomas. We have long recognized that apparently normal children may have occasional transitory cranial bruits. The bruit associated with some of the neoplasms, both vascular and those distorting major vascular trunks, tends to be consistent in character though not necessarily in degree of audibility. Waxing and waning of a bruit in the presence of tumor does occur, but the degree of variation is usually less marked in bruit related to new growth than when a physiological manifestation.

Somatic sensory change has been described in cerebral cortical lesions in childhood, but because of the requirements of cooperation and of language utilization, it is probably less manifest as a sign of disease than the lesions producing it would lead one to suspect. Somatic sensory changes were mentioned in only 7 per cent of the patients having supratentorial tumors in this series.

Examination of the patient is incomplete without the use of all available methods of differentiation. X-ray of the skull is the most common laboratory study employed. In the infant, the x-ray may confirm the presence of separated sutures, of enlargement of the head or of focal erosive changes, particularly about the base of the skull and in the region of the sella turcica. Erosion, either by direct pressure or by generalized increase in intracranial pressure, can be seen about the sella turcica in children in the older age groups, and this information may be of diagnostic value.

Calcification of an intracranial mass was demonstrated in 30 per cent of patients with supratentorial tumors, a percentage higher than anticipated. In half of these instances, the lesion was angioma, pinealoma, or Rathke pouch cyst. Epidermoid cysts within the cranium were next in number of calcified lesions. Calcification has also been seen in astrocytoma, meningioma, ependymona, polar spongioblastoma, hemangioendothelioma, and oligodendroglioma in childhood. The character of the x-ray pattern of calcification is seldom such as to permit prediction of the pathological nature of the neoplasm. More often localization of the calcified pattern, as in the case of pinealoma and Rathke pouch cyst, has seemed a more justifiable basis for opinion concerning the character of the growth.

Electroencephalograms, which have been employed in the later years of this series, have proved disappointing both as a differential study and as a localizing study. In a large number of children who have been studied since the advent of electroencephalography, tests have been omitted because of failure of cooperation of the child or because of other considerations. In the patients who have been studied, a normal electroencephalogram was found in three instances, a diffuse, nonlocalizing abnormality of the electroencephalogram was found in three, and the tracing was read as "questionable" in five. A correct focus was reported in twelve instances, if one allows the term "post-temporo-occipital abnormality" as correct for a lesion of the cerebellar hemisphere. Localization was flatly incorrect in seven instances; in eight cases it was near the lesion but not correct as to the area of the lesion.

Cerebrospinal fluid studies are rarely justifiable in tumors in childhood because of the dangers dependent on the taking of cerebrospinal fluid from the lumbar sac when there is obviously increasing intracranial pressure. Spinal fluid was usually not obtained, therefore, in patients with an obvious intracranial growth of any size. Spinal fluid studies were carried out in nineteen patients, and in nine of these the pressure was normal; in ten it was elevated. Ten patients had an increase in cerebrospinal fluid protein and in nine it was normal. In three patients there was an increase in cell count of the cerebrospinal fluid.

Pneumoencephalography, either by the lumbar or the ventricular route, was employed in the majority of instances and usually gave the correct localization when it was employed. It was not generally used where plain films of the skull showed calcification in a position to coincide with the clinical evidence of disease. In thirty-three patients with supratentorial tumors in which it was employed, the correct localization was found in thirty-one instances and an error made in two.

The recent advent of angiography has permitted the further elimination of error in the diagnosis of two groups of patients. For those with angioma and those with a vascular lesion which is not angiomatous in character, angiography is rapidly becoming an indispensable test.

SUMMARY

Brain tumors in childhood are found above the tentorium only slightly less frequently than in the posterior fossa. Generally speaking, these tumors

are more slow growing and have a better prognosis as to life than do those below the tentorium. Their early diagnosis remains a major problem.

Headache, vomiting, loss of vision, convulsive seizures, and ataxia are the more common presenting symptoms. The clinical signs which have been found frequently include papilledema, unilateral weakness of the extremities, increase in size or distortion of the head (in children under 5 years of age), nystagmus, and cranial bruit. Intracranial calcification was demonstrable by x-ray in 30 per cent of the patients.

The differential diagnoses include epilepsy, cerebral vascular accident, encephalitis, gastrointestinal upset, post-traumatic state, and "behavior disturbance."

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PATHOLOGIC LESIONS IN CYSTIC FIBROSIS OF THE PANCREAS

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AS OUR knowledge concerning the etiological factors underlying "celiac disease" has increased there has gradually evolved a distinct clinicopathological entity which deserves the designation of a separate disease; namely, cystic fibrosis of the pancreas. Since this is so, it follows that the term "celiac disease" should be replaced by the term "celiac syndrome" in order to avoid any sense of diagnostic finality on the part of the clinician, and to encourage the further identification of more distinct entities in this clinical group.

The establishment of cystic fibrosis of the pancreas as a valid subdivision of the celiac syndrome has been gradual. Certainly by 1913 Garrod and Hurtley[1] had associated this probable lesion with the congenital diarrheas of children, and much earlier than that the pancreas had been suspected in connection with the passage of fatty stools. The role of the pancreas in the celiac syndrome was slow to be demonstrated, however, since even as late as 1923 R. Miller,[2] in discussing the pathogenesis of "celiac disease," ruled out the pancreas as an etiological agent, "because it is usually normal." He concluded that the probable underlying defect was in the bile salts with consequent faulty fat absorption.

Although by no means the first author to describe cystic fibrosis of the pancreas in the literature, it was Parmelee[3] who proposed that this be established as a valid subtype of the celiac syndrome. This concept was accepted by many authors and efforts were soon made to differentiate clinically this pancreatogenous celiac disease from other types of the disease. Harper[4] and Rauch, Litvak, and Steiner[5] presented criteria for this differentiation as has Andersen[6] in a comprehensive review of the subject.

Cystic fibrosis of the pancreas has now been established as a clinicopathological entity, and with attention thus focused on it the number of cases reported has greatly increased. Knowledge of this disease has not kept pace with the number of reported cases. Much remains to be clarified, especially with regard to the pulmonary manifestations, the vitamin factors, and the severity and extent of microscopic lesions as compared to clinical findings. With these points in mind it is felt that a review and case study of the pediatric records and pathological specimens at the University of California Hospital would be profitable.

During a twenty-six-year period there were 10,775 admissions to the pediatric service with 658 deaths and 363 autopsies. A review was made of tissues from all children who had died with some of the clinical signs and symptoms of a celiac type of syndrome, regardless of the basic cause. In this diverse group of cases, about one out of four revealed microscopically various degrees of cystic fibrosis of the pancreas.

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TABLE I. FIBROCYSTIC DISEASE OF THE PANCREAS

U.A. NO.	SEX	AGE AT DEATH	DURATION OF SIGNS AND SYMPTOMS	PATHOLOGICAL FINDINGS				
				PANCREAS	LUNGS	LIVER	INTESTINES	OTHER
46-118 DDW	M	3 months	2 months; Cough; bulky pale stools	Fibrosis marked; mod. cystic acini and ducts; scattered round cells; islets normal	Bronchopneumonia; infrequent cystic bronchial glands	Negative	Brunner's glands—neg.; few dilated colon glands	Absent
45-148 DH	F	16 months	14 months; Cough; bulky stools	Marked fibrosis and round cells; moderate cystic ducts and acini; advanced destruction of acini	Bronchopneumonia; bronchiectasis; bronchial metaplasia	Negative	Brunner's glands—cystic	Absent
44-173 GAR	M	10 weeks	7 weeks; Dry cough; weight loss	Slight fibrosis ducts and acini slight dilation and with inspissated secretion	Bronchopneumonia with bronchiectasis, slight	Negative	Moderate dilation of Brunner's glands	Atrophic changes in salivary glands Lymph nodes: subacute adenitis
44-59 RS	M	2 years	About 1 year; Respiratory symptoms	Advanced fibrosis; cystic glands and ducts; islets normal	Bronchopneumonia with bronchiectasis	Negative	Brunner's glands—moderately cystic	Absent
44-32 GHF	M	5 months	3 months; Persistent cough; bulky yellowish stools	Much fibrosis with moderate numbers of lymphocytes; moderately cystic ducts and acini; islets not remarkable	Bronchopneumonia and bronchiectasis	Stenosis of cystic bile duct	Brunner's glands—moderately cystic dilation	Moderate thyroid fibrosis
43-112 NH	M	4 months	3 months; Cough	Moderately cystic; fibrosis and round cells; slight metaplasia; islets normal	Bronchopneumonia; bronchiectasis	Negative	Duodenal glands—cystic	Accessory spleen Lymph nodes: hyperplastic with chronic adenitis
43-55 RC	M	8½ months	3 months; Chronic cough; bulky pale stools	Extensive fibrosis and round cells; many cysts; islets normal	Bronchopneumonia with bronchiectasis; slight bronchial epithelial metaplasia	No fat; focal acute hepatitis with degeneration	Brunner's glands—cystic	Lymph nodes: subacute lymphadenitis

43-46 RB	M	8 weeks	7½ weeks; Productive cough; large B.M. 3 to 4 times daily	Slightly cystic; moderate fibrosis; islets normal	Bronchopneumonia with bronchiectasis; bronchial epithelial metaplasia	Normal	Brunner's glands—cystic	Lymph nodes: chronic lymphadenitis
42-179 ST	F	2 years, 3 months	1 year; Pertussis; foul, bulky, light yellow stools; fever	Not cystic with good ducts; moderate fibrosis	Bronchopneumonia, slight with bronchiectasis	Fatty infiltration and degeneration	Brunner's glands—cystic	Lymph nodes: chronic lymphadenitis Bilateral fusiform ovaries; epicardial fibrosis
42-163 CAN	F	11 months	6 months; Cough; fever; frequent foul stools	Slightly cystic; moderate fibrosis; islets normal	Bronchopneumonia; bronchiectasis	Bile duct proliferation; fatty infiltration	Brunner's glands—slightly cystic	Spleen: slightly hyperplastic Capillary hemangioma of skin
42-29 JM	F	16½ months	9 months; Cough; wheezing; frequent diarrhea	Small cysts; moderate fibrosis; islets good	Bronchopneumonia with abscesses; bronchiectasis	Fatty infiltration	Duodenum not sectioned	Lymph nodes: chronic lymphadenitis Adrenals: capsular fibrosis Kidney: pelvic epithelial metaplasia
37-32 WM	M	7 months	6½ months; Bronchopneumonia; foul, bulky, green stools	Moderately cystic and limited to ducts; metaplastic epithelium; islets good	Bronchopneumonia and bronchiectasis	Normal	Duodenum not sectioned	Lymph nodes: general lymphadenitis
MMH 36- LY	M	12 years	5 years; Productive cough; large frequent "porridge-like" stools	Much fibrosis and many cysts; islets normal	Bronchopneumonia and bronchiectasis; tracheal epithelial metaplasia	Cirrhosis; fatty infiltration, slight	Brunner's glands—slightly cystic	Spleen: fibrosis and plasma cell infiltration Lymph nodes: chronic and subacute lymphadenitis
35-62 DD	F	18½ months	17 months; Persistent cough; foul, soft, yellow stools	Moderately cystic ducts; some dilatation; much fibrosis; islets good	Bronchiectasis	Fatty infiltration of liver	Duodenum not sectioned	Patent ductus arteriosis
32-10 PC	F	10 months	3½ months; Persistent cough; liquid green stools	Markedly cystic ducts with much fibrosis; islets good	Bronchiectasis with abscesses and metaplasia	Fatty infiltration of liver	Duodenum not sectioned	Lymph nodes: chronic lymphadenitis Thymus: hyperinvoluted Bilateral mastoiditis

TABLE I—CONT'D

U.A. NO.	SEX	AGE AT DEATH	DURATION OF SIGNS AND SYMPTOMS	PATHOLOGICAL FINDINGS				
				PANCREAS	LUNGS	LIVER	INTESTINES	OTHER
31-93 FB	M	5¼ months	5 months; Foul, frothy green stools	No cysts; moderate interlobular fibrosis; islets good	Slight bronchopneumonia	Moderate fatty infiltration	Normal	Spleen: myeloid hyperplasia. Thymus: hyperinvoluted
31-57 BJH	F	22 months	6 months; Cough; foul yellow B.M., protuberant abdomen, clubbing of fingers and toes	Duct ectasia; moderate interacinar fibrosis; islets good	Bronchitis and bronchopneumonia; metaplasia	Bile duct proliferation; no fat	Duodenum not sectioned	Lymph nodes: chronic inflammation Bladder: metaplasia of epithelium
30-57 BGR	F	20 days	20 days; Râles at lung bases; yellow watery stools; steady weight loss	Not cystic; moderate interacinar fibrosis. Ducts normal, acini slightly ectatic	Doubtful bronchiectasis and slight pneumonia	Normal	Duodenum not sectioned	Lymph nodes: chronic inflammation with many eosinophiles Left otitis media
28-522 RW	M	2½ months	2½ months; Cough; fever; râles in lungs; frequent dark green stools	Not cystic; much fibrosis; some ectasia of acini; islets good	Bronchopneumonia; bronchiectasis	Fatty infiltration	Duodenum not sectioned	Lymph nodes: lymphadenitis Thymus: hyperinvoluted, slight
25-56 BB	M	5 months	3 months; Cough; greenish stools with mucus	Moderate cysts; moderate fibrosis	Bronchopneumonia and bronchiectasis	Fatty infiltration	Duodenum not sectioned	Lymph nodes: normal

Twenty cases of fibrocystic disease of the pancreas were thus encountered and were reviewed (Table I), with particular attention being directed toward the detection of evidence of lesions in other organs than the pancreas and lungs. In the earlier autopsies sections were not taken of certain pertinent tissues, for instance the duodenum, so that the status of any lesions that it may have had could not be ascertained. In all of the cases in which duodenal sections were examined various degrees of dilation were encountered. Thus definite cystic lesions of the Brunner glands were the rule in this disease. These lesions, however, were never so striking as the pancreatic changes. In one case a few cystic changes in the mucosal glands of the large bowel were seen. Another autopsy revealed atrophic, fibrotic, and slight ectatic changes in the salivary glands. Since these structures were seldom examined in the earlier cases no indication of the frequency of such abnormalities can be had.

In the liver, fatty infiltration was the rule, which doubtlessly is on the basis of terminal nutritional conditions. In addition, however, four of the livers showed cirrhotic processes or bile duct anomalies. Apparent congenital anomalies included one case each with accessory spleens, abnormal ovaries, cutaneous hemangioma, and patent ductus arteriosus.

In most cases reactions to a debilitating disease with secondary bacterial invasion were encountered. A low-grade lymphadenitis, hyperplastic spleens, and bone marrow, and apparent involuted thymus responses were often present. Most of the foci of epithelial metaplasia were located in the lungs near areas of extensive inflammation and were more than likely due to the inflammatory stimulus.

The pulmonary lesions were completely consistent and typical. The striking lesion was near and in the bronchus. It was extensively inflamed, often dilated, and with a partially ulcerated wall. Pools of leucocytic debris were found throughout this area and extended from here out into the surrounding alveoli as a variably severe bronchopneumonia. As indicated, some bronchial epithelial metaplasia was the rule if carefully looked for. Also various degrees of atrophy or cystic dilation of the mucous glands of the bronchi were usually present. Examination of the ciliary action of the bronchial mucosa from fresh tissues of three autopsies revealed brisk motion.

The pancreatic lesions were most characteristic. The degree of destruction of its architecture varied greatly, and it was impossible to correlate the extent of the injury with the apparent clinical severity of the disease. It was clearly evident that, in general, the younger the patient at the time of death, the less severe were the structural abnormalities of the pancreas and probably, to a lesser extent, of the other involved organs of the body. The fibrosis of the pancreas seemed to cause little damage to the islet tissues. Some atrophy and stenosis of the pancreatic duct was encountered, but this was usually not evident. Although the dilated and cystic pancreatic glandular elements were sometimes seemingly filled with morphologically dark material, tests to determine their true viscosity and density were not done.

DISCUSSION

In many respects the twenty autopsy reports reviewed in this study correspond to those presented in the literature. The ages varied from 20 days to 12 years, and there was no significant tendency to be related to any one sex. All of the children belonged to the white race, and in this series there were two instances suggestive of familial tendency evident at the time of hospital entry. No increase in the incidence of the disease has been noted in this hospital in recent years as judged by all autopsy findings, which routinely include sections of the pancreas.

A review of the microscopic sections from the standpoint of correlating the extent of pancreatic parenchymal destruction with the severity of the celiac syndrome symptoms failed to reveal any apparent correlation between the two. The least involved pancreas microscopically was from the 20-day-old infant. Other than that, no lesions which varied with the age of the patient were noted. The pulmonary pathology was approximately parallel in severity with the clinical pulmonary signs and symptoms.

These findings deserve further consideration. The absence of apparent correlation between the degree of pancreatic involvement and the severity of the celiac syndrome should serve to emphasize the fact that the celiac syndrome results from many factors and may be produced by any combination of the following factors: abnormal or faulty bile function, pancreatic anomalies, abnormal succus entericus, faulty intestinal absorption and rapid passage of contents through the intestine. Further evidence against an exclusively pancreatic dysfunction is the fact that experimentally 10 per cent of the pancreas is sufficient to maintain pancreatic competency (Greenberg[7]). Although the microscopic estimation of the percentage of parenchymal destruction is difficult, it is estimated that in only five instances was as much as 70 to 80 per cent of the parenchyma destroyed. In eight cases about 50 per cent of the pancreas was considered present, and in four, 10 to 20 per cent of the acini were microscopically abnormal. Eosinophilic cellular granules were always present in some cells and were more abundant in the more normal appearing glands. As is the case with other glands of the body, it may be impossible, except in extreme cases, to correlate the finer microscopic details with variations in function.

That the pancreas may be almost completely absent and yet unaccompanied by a celiac syndrome has been demonstrated in children (Davie[8]). Adults may not reveal a celiac syndrome until very extensive (90 per cent or greater) acinar destruction has occurred. These facts serve to suggest that probably the succus entericus may be able to carry a great proportion of the digestive load. Certainly the intestinal secretions, being enzymatic, should be able to handle relatively large amounts of chyme. In fact, Hansman[9] remarks that the "excess of intestinal lipase is so great that it must seldom happen that, even in the absence of pancreatic secretions, the fats are not hydrolyzed, unless for mechanical reason."

These facts suggest that abnormalities may be present in the intestinal tract in cystic fibrosis of the pancreas which prevent any compensatory effects

on digestion by the succus entericus. Usually no microscopic clue of such an intestinal dysfunction is found, although some instances of cystic changes in Brunner's gland have been reported by Raser and Stevenson[10] and were found in all of the autopsies in which duodenal tissues were examined microscopically. Doubtless more examples would be found if searched for, since in all of our cases in which the duodenum was sectioned varying degrees of cystic Brunner's gland were found. The duodenal drainage studies of Andersen[11] and Gibbs,[12] and the variations which have been reported in the stool fats, must be a reflexion of both pancreatic and intestinal glandular insufficiencies. Certain facts suggest that, in addition, defects in intestinal absorption exist.

At times the fats of the food are completely split, as judged by stool analyses, and yet the celiac symptoms and abnormal absorption have persisted. It is probable that many of the low vitamin A titers which these patients possess reflect faulty absorption, although in two cases parenteral vitamin A was given without effect on the blood level. In these two cases this may reflect loss of ability of utilization or may represent very poor local absorption. Snelling[13] and others prefer to relate vitamin A deficiencies more directly with the etiology of the disease.

The presence of epithelial metaplasia has received different degrees of emphasis. It was found in several instances in the lungs and pancreas of patients presented in this paper, and in relationship to extensive chronic inflammatory reactions. In inflammation some epithelial metaplasia can be expected. Under such conditions metaplasia should be used only with caution as particular evidence in favor of vitamin A deficiency.

Etiological Considerations.—Further investigations may identify two basic factors underlying this disease; one being essentially a congenital defect, and the other having an inflammatory background. The congenital defect concept has received the most active support and has much to commend it. The familial tendency is well established although not always evident. Within families, several types and degrees of the celiac syndrome may exist, and variations in the type of pancreatic enzymatic deficiencies may be apparent (Gibbs[14]). These different gradations in pancreatic insufficiencies speak rather for variations in development than inflammation. Additional evidence is the association with other structural anomalies. Pancreatic duct atresias, cardiac anomalies, bile duct proliferation and atresias, prolapse of the rectum, Meckel's diverticulum, and ovarian anomalies have been reported. The clinical examples most likely to be on a congenital malfunction basis are the infants who died in the first few weeks of life. At that age there is not sufficient time nor microscopic evidence of the existence of an infectious process. Evidence of an intrauterine infection is not seen, so that the actual cause of the congenital anomaly lies in the field of pure speculation.

Whereas most of the pancreatic lesions are present from birth, as judged from the neonatal onset of symptoms, the possibility of a postnatal origin cannot be excluded. The picture of cystic fibrosis of the pancreas is found in the adult. Darkinski[15] noted parenchymal degeneration which had advanced to acinar

cyst formations in necropsies on adults who died of toxemic types of diseases. The inflammatory cause in most of these adult patients need not be doubted. Such a basis is a definite probability with some of the cystic fibroses of the pancreas. More specific support of this possibility is the presence of generalized chronic adenitis in many cases. Also, the generalized inflammatory background of the pulmonary lesions may be a factor in the progression of the disease in the pancreas. This possible division in the etiological factors of the pancreatic lesion serves no concrete purpose at present because they cannot yet be separated clinically. However, it may be that those with an especially marked secondary inflammatory reaction, particularly in the lung, may prove to be the ones most aided by present therapeutic efforts and might thus be well worth identifying.

The relationship between the pulmonary and pancreatic lesions is still obscure. The absence of bronchiectasis, fibrosis, or extensive inflammation in the infant dying at the age of 20 days corresponds to the usual findings reported in the literature. In older children and adults, extensive pulmonary abscesses, inflammation, and bronchiectasis are seen. These age differences suggest that the disease is a progressive one and that the passage of time leads to increased tissue change. The pulmonary lesions are not characteristic or extensive in the neonatal period of cystic fibrosis of the pancreas. The characteristic lesions develop later and are associated with the continued use of the lungs and exposure to infections.

A common factor which would explain the many lesions found in fibrocystic disease has long been searched for, and several have been suggested. One of the earliest explanations was that these patients suffered from a vitamin A deficiency. This has not been proved, so that endocrine abnormalities or even generalized allergic responses have been postulated. Especially popular is the concept that the underlying abnormality in this disease is a dysfunction of the serous and mucous glands of the body. It has been supposed that perhaps certain enzymes, perhaps especially mucolytic ones, are at fault leading thus to inspissated, tenacious secretions with all of the resultant structural and functional effect that such material might have on many serous and glandular areas of the body. Methodical studies of such possible factors should clarify the status of this concept.

SUMMARY

The autopsy findings of twenty case examples of fibrocystic disease of the pancreas are reviewed, and the pertinent data is recorded in chart form. A short résumé of the literature on this disease is included with an emphasis on the desirability of using the term celiac syndrome instead of the designation of celiac disease. There were twenty cases of fibrocystic disease of the pancreas encountered in 363 autopsies from a total of 10,775 admissions to the Pediatric Service of the University of California Hospital. It is noted that there is no apparent correlation between the microscopic appearance of the pancreas and the severity of the clinical syndrome. This suggests that factors of absorption, enteric insufficiency and anomalous function, etc., contribute to the development of the clinical picture.

Therapeutic efforts have been consistently disappointing, even in the clinically early cases, and autopsies of patients treated by the newest regimen have presented essentially the same morphological lesions as in untreated cases.

This is a disease often involving many glandular organs, besides the pancreas and lungs. Liver anomalies, salivary gland lesions, and cystic changes in the intestinal mucous membrane may be encountered. Simple secondary bacterial infection must be a factor in the progress of the disease, especially in the lungs. A more fundamental factor, however, is probably at work. Several possibilities exist, but current studies directed toward the elucidation of the chemical and enzymatic details of mucin production seem especially pertinent.

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INFECTIONS OF THE CENTRAL NERVOUS SYSTEM: AN APPROACH TO DIAGNOSIS

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ONE of the commonest and most difficult problems arising in infectious disease practice is that of the differential diagnosis of infections of the central nervous system. With the advance of clinical observation and laboratory techniques, an increasing number of specific disease entities have been included in this group which require differentiation. Furthermore, since specific treatment is available for at least some of these diseases, early accurate diagnosis is essential so that therapy may be directed intelligently.

As a basis for understanding the complexity of the problem, it is essential that infections of the central nervous system be classified into groups having similar causation and clinical pictures (Table I). Such a division into purulent meningitis, granulomatous meningitis, and viral infections, in spite of certain shortcomings, will facilitate the approach to diagnosis and treatment. In addition to the diseases included in this classification, certain other processes involving the central nervous system must also be differentiated. Included in this group are brain abscess, brain tumor, infectious neuronitis, neighborhood reaction to septic foci in the skull or spine, and various vascular lesions. Furthermore, certain diseases not actually involving the central nervous system, but producing manifestations which might be ascribed to such involvement, must also be considered. In this group are meningismus, rheumatic fever, and various disorders of the locomotor system.

Certain symptoms and signs are common to many or all infections of the central nervous system and their presence should always arouse sufficient suspicion of such disease to warrant lumbar puncture and other special diagnostic procedures. Headache or disturbance of the state of consciousness should always suggest the possibility of central nervous system infection. Such physical findings as stiffness of the neck and back and limitation of straight-leg raising (or positive Kernig's maneuver) occur in the great majority of such infections.

History.—Certain elements may be elicited in the history which will aid in differentiation. Of considerable value at times is information of an epidemiological nature. In some areas poliomyelitis is sharply seasonal in its occurrence, and diseases occurring during the winter are most unlikely to be due to poliomyelitis virus. This is considerably less true of climates lacking marked seasonal differences in temperature. Similarly arthropod-borne encephalitis can exist only in areas where the insect vector, generally certain limited species of mos-

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TABLE I. CLASSIFICATION OF DIFFUSE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

PURULENT MENINGITIS	GRANULOMATOUS MENINGITIS	VIRAL INFECTIONS
Meningococcal	Tuberculous	Poliomyelitis
Pneumococcal	Coccidioidal	Arthropod-borne encephalitis
Streptococcal	Cryptococcal	Postinfectious encephalitis (?)
Staphylococcal	Syphilitic	Mumps
Hemophilus influenzae	Other	Lymphocytic choriomeningitis
Other		Rabies
		Coxsackie disease
		Infectious mononucleosis (?)
		Other

quito, is present, and only at such times of the year when the vector is active, usually in the summer. Coccidioidal meningitis can occur only in persons who have been in an endemic area in the recent past. The history of known or suspected tuberculosis contact may be of great aid. Conversely, contact history is quite uncommon in meningococcal meningitis.

Information concerning any illness preceding infections of the nervous system is important, especially in regard to tuberculosis and syphilis. In addition, the history of discharging ears, sinusitis, or suppurative pulmonary disease may lead to suspicion of spread to the central nervous system. The abruptness of onset of symptoms of the nervous system process is also helpful. Most instances of purulent meningitis are of abrupt onset, whereas the onset of granulomatous meningitis is likely to be more insidious. Poliomyelitis, post-infectious encephalitis, and certain other viral infections may be preceded by a distinct prodromal illness. The history of convulsions, which is common in many nervous system infections, is rare in poliomyelitis.

Physical Examination.—In the vast majority of central nervous system infections, the so-called "signs of meningeal irritation" will be present. Only in the terminal state or in infants is stiffness of the neck and back and tightness of the hamstring muscles likely to be absent. In infants bulging of the anterior fontanel is an additional sign. Most commonly the neck is rigid and little or no forward flexion is possible in patients who have purulent or granulomatous meningitis. On the other hand, in poliomyelitis and other viral infections a free range of forward flexion is commonly noted before tightening of the neck extensors occurs.

The state of consciousness of the patient may be of diagnostic aid. Characteristically, although far from uniformly, depression of the consciousness is noted in purulent meningitis, granulomatous meningitis, and encephalitis. Conversely, pronounced disturbance of the sensorium is relatively uncommon in poliomyelitis and mumps meningoencephalitis.

A petecheal rash in the presence of meningitis is strongly suggestive of meningococcal etiology, although such rashes are occasionally observed in other types of purulent meningitis. The petechiae of acute bacterial endocarditis may occur in association with septic embolism of the brain and may mimic meningococcal meningitis. The presence of significant heart murmurs, splenomegaly, and splinter hemorrhages in the beds of the nails are indicative of a cardiac

origin of the process. The rash of one of the exanthemata or a recent vaccination should lead to strong suspicion of postinfectious encephalitis.

The demonstration of a focus of infection outside the central nervous system is very important. Otitis media, mastoiditis, or sinusitis are most commonly associated with streptococcal, pneumococcal, or staphylococcal meningitis, although tuberculous or other types are occasionally observed. Pneumonia in the presence of meningitis is presumptive evidence of pneumococcal etiology. The demonstration of tuberculosis in the lungs or elsewhere is of extreme diagnostic importance. The peculiar statistical coincidence of cryptococcal (torula) meningitis and Hodgkin's disease[1] may occasionally be of aid. Salivary gland enlargement is generally observed in mumps meningoencephalitis, but occasionally central nervous system invasion is the sole manifestation of mumps.

Although in many instances neurological abnormalities other than the signs of meningeal irritation may be lacking, certain signs may be of great diagnostic significance. Lower motor neuron paralysis associated with diminution or loss of tendon reflexes is seen almost exclusively in poliomyelitis, although infectious neuronitis and infection due to Coxsackie virus[2] may cause confusion. Conversely, upper motor neuron lesions almost never occur in the course of poliomyelitis. Lesions of the third, fourth, and sixth cranial nerves are exceedingly common in tuberculous meningitis, are not rare in encephalitis, but are rather uncommon in poliomyelitis. Muscle "spasm," which is so prominent in poliomyelitis, may also be present in some degree in other infections of the central nervous system, although rarely to the extent or for as long a period as is observed in poliomyelitis. Persistence of muscle spasm over a period of two or more weeks is highly suggestive of poliomyelitis.

Laboratory Examination.—The laboratory furnishes great aid in the differentiation of infections of the central nervous system. The white blood cell count is usually sharply elevated in cases of purulent meningitis, but is more often relatively normal in granulomatous and viral infections. The blood culture is often a welcome means of isolating the causative agent in purulent meningitis, but is negative in other forms of central nervous system infection.

The examination of cerebrospinal fluid[3] is the most important single procedure in the study of this group of infections. Moreover, maximum information may be obtained only by a complete examination (Table II). The cerebrospinal fluid pressure is usually greatly elevated in purulent and granulomatous meningitis and will usually be found to be so on repeated daily lumbar punctures. On the contrary, viral infections rarely produce marked or persistent pressure elevations.

The character of the cellular exudate is of greatest importance. It must be recalled, however, that chemotherapeutic treatment of purulent meningitis alters the characteristic picture so that lymphocytes may predominate after several days. In the early stages of granulomatous and viral infections, polymorphonuclear leucocytes may predominate, to be succeeded later by lymphocytes. While in most cases of purulent meningitis more than 1,000 cells per cubic millimeter are observed, exceptions are not rare. On the other hand, large num-

TABLE II. TYPICAL FINDINGS OF CEREBROSPINAL FLUID IN VARIOUS CENTRAL NERVOUS SYSTEM DISEASES

TYPE OF PROCESS	CELLS PER CU. MM.	CELL TYPE†	PRESSURE	PROTEIN MG. %	GLUCOSE MG. %	CHLORIDE MG. %	ETIOLOGICAL AGENT
Purulent meningitis	> 1,000	PMN	++++	> 100	< 40	< 720	Readily isolated
Granulomatous meningitis	< 1,000	L‡	+++	> 100	< 40	< 720	Isolated with difficulty
Viral infection	< 1,000	L‡	Normal +	< 100	> 40	> 720	0
"Neighborhood" reaction*	Variable	Variable	Variable	Variable	> 40	> 720	0

*May occur in mastoiditis, sinusitis, brain abscess, brain tumor, epidural abscess.
†PMN = polymorphonuclear; L = lymphocyte.
‡PMN may predominate early.

bers of cells are seen occasionally in granulomatous and viral infections. As high as 2,100 cells per cubic millimeter, 85 per cent of which were polymorphonuclear leucocytes, has been observed in poliomyelitis. Over 1,000 lymphocytes per cubic millimeter are more likely to be seen in mumps meningoencephalitis or lymphocytic choriomeningitis than in other viral infections, although lower counts are the rule in all infections due to viruses. Complete absence of pleocytosis has been observed in poliomyelitis, and probably occurs in other viral infections as well. It is well known that pleocytosis may occur in the presence of brain abscess or tumor, or due to neighborhood reaction to septic foci in the skull or spine.

Determination of the glucose content of the cerebrospinal fluid is an essential part of the examination. Characteristically, the glucose level is decreased in purulent or granulomatous meningitis and is normal in viral infections. Since the glucose may be normal at the outset in the former groups, repeated determinations may be necessary in doubtful cases.

Although the chloride content of the cerebrospinal fluid is reduced in purulent meningitis, this determination is of greatest value in differentiation between granulomatous meningitis and viral infections. Marked reduction occurs in tuberculous and coccidioidal meningitis, although the reduction of glucose content usually is noted earlier. Normal values for glucose and chlorides are common in syphilitic meningitis. This emphasizes the importance of the Wassermann reaction of the cerebrospinal fluid in all cases of granulomatous meningitis.

The protein content of the cerebrospinal fluid may also be of aid in diagnosis. Significant elevations are usually encountered in purulent and granulomatous meningitis but are uncommon during the early stages of viral infections. The albuminocytologic dissociation of so-called infectious neuronitis is an important diagnostic feature, but may appear late in the course of poliomyelitis.

The colloidal gold curve is of very limited value in the differentiation of infectious processes. Normal or variously altered values are seen in all types of infections. The high first-zone curve of coccidioidal meningitis is characteristic, however.

The demonstration of the etiological agent in the cerebrospinal fluid is obviously of the greatest diagnostic significance. Appropriate cultures should be made in all instances of purulent meningitis. While a properly stained smear of the centrifuged fluid often will reveal the causative agent, such smears should be interpreted with the greatest caution as diagnostic errors are surprisingly common. If no organisms are observed in the smear of a purulent spinal fluid, a meningococcal etiology is probable.

The demonstration of *Mycobacterium tuberculosis* in the smear of the spinal fluid, even in the pellicle, is far from easy. Appropriate media, as well as guinea pigs, should be inoculated, but treatment may be instituted before bacteriologic proof is available. *Coccidioides immitis* and *Cryptococcus hominis* may readily be mistaken for lymphocytes in the cerebrospinal fluid on causal inspection. Sabouraud's medium and guinea pigs should be inoculated in all cases of suspected granulomatous meningitis.

Since the demonstration of tuberculosis, coccidiomycosis, and other important foci of infection outside the central nervous system may be of great inferential diagnostic value, maximum use of x-rays and skin tests should be made. In a child a positive tuberculin reaction is highly suggestive of active tuberculosis, although in an adult the significance is much less. Both tuberculin and coccidioidin skin tests may be negative in disseminated forms of these infections. In the instance of coccidiomycosis the demonstration of high precipitin or complement-fixing antibody titers may allow the correct diagnosis.

Certain serologic procedures are available in a limited number of infections. The Wassermann reaction of syphilis and the sheep cell agglutination reaction of infectious mononucleosis are widely used. A rise in antibodies against the viruses of Eastern and Western equine encephalomyelitis, St. Louis encephalitis, lymphocytic choriomeningitis, and mumps may be discernible by comparing the titer of serum drawn near the onset of the illness with serum drawn two to three weeks later. It is important in all central nervous system infections of doubtful etiology that the initial or "acute" blood specimen be drawn, allowed to clot in a sterile tube, and then refrigerated. A high antibody titer in a single late blood specimen is not sufficient for diagnosis. Unfortunately, practical serologic procedures are not available for the diagnosis of poliomyelitis and infections due to Coxsackie virus. The isolation of viruses from the blood, tissues, or, in the case of mumps and lymphocytic choriomeningitis, from the cerebrospinal fluid is not a practical clinical procedure.

DISCUSSION

If the problem of differential diagnosis of infections of the nervous system is approached systematically, little difficulty is to be expected in the exact etiological diagnosis of purulent meningitis. The diagnosis of granulomatous meningitis offers a somewhat greater problem in that viral infections must first be excluded, principally on the basis of the reduction in cerebrospinal fluid glucose and chloride levels. Further differentiation among the group requires careful cultural studies, animal inoculation, and skin tests, as well as evaluation of the condition of the patient as a whole. The clinical differentiation of the various

viral infections of the central nervous system offers a much more difficult and, at times, insoluble problem. Mild forms of any of the viral infections may be identical clinically. Since definitive treatment is not yet available for this group, exact etiological diagnosis is principally of importance from a public health standpoint.

SUMMARY AND CONCLUSIONS

1. Infections of the central nervous system may be classified as (a) purulent meningitis, (b) granulomatous meningitis, and (c) viral infections.

2. Other localized diseases of the central nervous system and certain infections outside the central nervous system may mimic the clinical picture of diffuse central nervous system infection.

3. The correct diagnosis may be made in most instances by careful attention to certain features of the history and physical examination, and intelligent use of laboratory and x-ray facilities.

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PSYCHOTIC BEHAVIOR IN A CHILD

Case Report

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PSYCHOTIC reactions in children, though no longer a rarity in the literature, are still unusual enough to justify reporting. The present case has a somewhat special interest, because the child was studied at the age of 5 years before the onset of any clear psychotic manifestations, and has been under observation at the Sonoma State Home during the past ten years.

The story of this boy's family background, the anxieties and fears present from infancy, and his own inability to adapt to the conditions surrounding him offer ground for speculation as to the various causes of his reaction, and raise questions as to the possibilities for treatment when the earliest signs of failure in normal social relations become evident.

Manuel's parents were both born in Puerto Rico and were of Spanish descent. Neither had any formal education, and before their marriage, which occurred when the father was 20 and the mother 18, the father had worked irregularly as a common laborer, and the mother as a domestic. Soon after their marriage they moved to Hawaii where the first of their eight children was born. A year later they moved to California where they have since lived. During the next twelve years, seven more children were born, and the economic situation of the family steadily went from bad to worse. The father, barely able to support himself before marriage, finally gave up his sporadic efforts to find work and solaced himself with alcohol. He was abusive to the mother and children, and by the time five children had been born, the whole family was in need of public relief. The mother, though without education, and speaking litfle English, was a quiet person of considerable refinement, devoted to her children and willing to cooperate intelligently with the various social agencies which provided for the needs of the family.

In 1932, Manuel was born, the seventh of the eight children. The pregnancy was stormy, the mother had a rheumatic heart, and developed such severe toxic symptoms that a therapeutic abortion was advised, but refused. Labor was finally induced at eight months; the birth was otherwise normal and birth weight was six pounds. During the first few weeks of life, he was described as a fussy infant who was restless at night, and during the first two years of life he had numerous illnesses, frequent colds, chronic otitis media, several attacks of bronchitis, and severe attacks of pneumonia. In spite of much ill health, early development was normal and training was uneventful. When the boy was 4 years old, the father was sent to a mental hospital as an alcoholic and the mother's cardiac condition became so serious that she could no longer manage the house-

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hold and supervise her many children. The five younger children were placed out of the home and Manuel and his 3-year-old sister were moved together to a small home for little children. Here he was described as a very quiet child who seldom smiled or laughed. He talked about the father's mistreatment of the mother, worried for fear the mother would not recover, and generally appeared more anxious and serious than the average child of his age. He played willingly but unenthusiastically with the other children and seemed to enjoy listening to stories, playing with the wagons and tricycles, and spent much time in his clay modeling.

When tested at 5 years of age, he cooperated well, seemed very anxious for approval, and was quite obviously disturbed when he thought he had made a mistake. His intelligence quotient was 97, in spite of the fact that Spanish was the language used in the home.

The 3-year-old sister was less bright than he and was much more aggressive and difficult to manage. On the other hand, she laughed and chattered at her play in a thoroughly normal manner.

Shortly after this, because of the mother's continued disability, Manuel and his 10-year-old brother were placed in a foster home. This foster mother was an energetic person who was often impatient with the boys and who regarded them both as abnormally shy and retiring, although Manuel was said to be the more talkative of the two. While on a brief visit to his mother, the boy complained that the foster mother yelled at him and frightened him, and his mother reported that the boy seemed to be becoming progressively more silent and restless. The two boys were promptly placed in a different foster home where two of their sisters were already living. This foster mother was easy-going, made few criticisms of the children, and did not expect too much of them.

Meanwhile Manuel and the other younger children had entered a parochial school where they were regarded as dull but not troublesome. Manuel learned more easily than his brother and sister and seemed happy with the companionship of other children. When at home he also played with the neighborhood children and appeared to enjoy normal childish social activities. Except that he had always been a quiet, serious, sensitive child, with more anxiety over his family situation than is usual in a boy of this age, he was not regarded as abnormal.

However, when he was 6 years old and finishing his first grade in school, more unusual behavior began to be manifest. He often remained alone in the house when the other children were at play, had uncontrolled screaming spells when angry, and when his mother visited the children he begged to go home with her. The older girls were with the mother, since they could help with the housework, and since the boy seemed so disturbed, plans were made to move the mother into larger quarters where he could be with her. He was told that he was to live with his mother very soon, and thereafter still stranger behavior became apparent. He could seldom be persuaded to go outside of the house to play at all and began following the foster mother around the house. When she insisted that he go outside to play, he obediently left the house, but paced back and forth in the yard and on several occasions placed a box outside of her window, climbed

up on it and stared at her. Once he waked in the night, crying, and said that he had dreamed his mother was dead. On another occasion he told his sister that his mother had stolen from the foster mother's landlord. The boy's confusion and anxiety showed clearly in his apparent inability to give up the foster home, though his expressed wish to be with his mother was being granted. Possibly the contrast between the overcrowded, poverty stricken home, with a mother in poor health and older sisters largely in control, and the relatively comfortable, well-regulated, though easy-going, foster home was vaguely evident to this sensitive, retiring boy. Whatever the underlying causes, his return to his mother's home was followed by increasing difficulties. Although attending school regularly, he seemed to gain nothing. Frequent outbursts of angry screaming were followed by tears. He often said that he was going to die, that he hated everybody, that his mother was not his real mother. He paced back and forth, trembling and twitching at times, and at other times he would jump up and down for minutes at a time. Sometimes he would grab his mother and try to shake her, and when other children tried to play with him he ran from them. He was often seen to spit on the back of his hand and then to lick it. As weeks passed he became more and more indifferent to what was happening about him and rarely spoke to anyone.

Finally, at the urgent request of the school, he was brought to the clinic for study. The mother had been apprehensive about bringing the boy and said that she had hoped that he would improve, but stated that she had finally become so exhausted caring for him and her other children that she had to get help for him.

On his first clinic visit, the boy was very unresponsive, spoke only rarely and in a hoarse whisper, and for the most part stared at his interviewer with complete disregard of anything said to him. He kept up a continuous tapping with his fingers on the table and once jumped suddenly from his chair, threw back his head and stiffened his whole body. On leaving, when good-bye was said to him, he turned abruptly and said, "Hello." A few days later, when again in the clinic, he was completely mute, but when given paper and crayons, covered sheet after sheet with a variety of geometric designs ornamented with scallops, fringes, and numerous small circles.

There were at that time no suitable facilities for caring for so disturbed a child, and athough the superintendent of one of the state mental hospitals had agreed to try to care for him and to try treatment, the mother objected and insisted on keeping him at home. However, he continued to be mute, refused practically all food, and several weeks later was admitted into the state mental hospital. Here he gradually improved, but was so little like a normal 8-year-old child, that transfer to the state school for mental defectives was recommended. His mother again took him home and he was admitted to the ungraded school. Here, however, he was able to cooperate for only brief periods of time and frequently interrupted whatever task he was engaged in by breaking out with snatches of songs or nursery rhymes. His mother finally requested that he be sent to the state school for defectives, and at 8 years of age he was admitted.

On admission, the boy was so rambling in speech and so confused, so unable to enter into any cooperative plans that school training and participation in occupational and recreational activities were at first entirely impossible. Gradually, however, he began to show interest in his surroundings, and at 9 years of age he entered school, which he attended for eight years. His behavior during most of this time was much like that noted when he was a small child in the children's home at the time of his mother's illness. He was very quiet, completed every task assigned to him with never a sign of resistance or resentment, but was slow both physically and mentally. He participated in sports willingly and performed well, but never with interest or enthusiasm. He also took part in some of the dramatic performances arranged for the children on holiday occasions. There were no evidences of compulsive or erratic behavior, merely an acceptance of anything planned or suggested to him. When tested for educational achievement at 18 years of age, his grade levels varied from fourth grade in arithmetical reasoning to sixth grade in language usage.

At 16 years he had been assigned to work as a helper in the laundry and continued with this work for more than a year. He worked willingly, but complained frequently of feeling "sick" and having headaches. At present he helps in his cottage in a somewhat supervisory capacity, seeing to it that the other boys have made the beds properly and have swept the floor clean.

During the Christmas holidays and for a summer vacation, he returns to his mother's home, where he helps a little with the housework and small chores out of doors, goes to an occasional movie, and rides around on his bicycle. He listens to the radio and comments that it keeps him occupied. He especially enjoys serial stories like "Gang Busters," popular music, and "give-away" programs.

The results of intelligence tests during the past year have been fairly consistent, and resemble those of the high grade mental defective more than those of the psychotic. On verbal tests, his level is that of the borderline defective, with intelligence quotients of 76 (Stanford, Form L), and 73 and 77 on the two verbal forms of the Wechsler-Bellevue Scale. On nonverbal tests, his performance is within normal limits. Actually, his mental capacity seems compatible with useful work, and is not much lower than that of some of the other children in his family who have been tested. His principal defect lies in his general attitude toward himself and toward life. His manner is one of caution and general apprehensiveness, although there is considerable response to encouragement and warm friendliness. His responses on the pictures of the Thematic Apperception Test are eloquent of his own problem. The picture of the boy with the violin is interpreted as a boy who "is thinking how good he'd do in the future, but it could be that he doesn't want to because it's too hard." Another picture with a boy sitting at a desk with a book is described as follows: "It looks like the boy is thinking of something he'll be when he's big. It could be that something is too hard for him." On the Rorschach examination there was a definite preoccupation with the shading on every card, even those where the color elements were most conspicuous. Several times he described land that is so far away that one can hardly see it, mountains that are "far, far off," a

desert that is far away. Rorschach regarded this tendency as "correlated with feelings of insufficiency—of being 'out of joint' with the times."

Quite apart from test records, this boy's whole attitude presents a picture of listlessness and general anxiety, with a lack of energy and avoidance of practical reality. He would like, he says, to leave the institution and return home permanently. He thinks he is good with handwork, but can suggest as possible vocations only art and music, in neither of which fields he has shown any ability. Both are sufficiently far away to offer no threat, whereas he expresses a lack of interest in simple manual work which might be within the range of his capacities. Probably his present life, which requires little expenditure of energy and which makes few demands on him, represents the easiest adjustment for him, and it is not very likely that efforts to parole him and to fit him into a vocational scheme in the outside world in which he will be effective and contented will meet with success.

The question of a diagnosis in this case, though not too important, is still of interest. His early, totally disruptive behavior definitely suggested a psychosis, although many of his actions were of a compulsive, defensive sort, interspersed with panic states. At present, his behavior indicates the same anxious, apprehensive attitude which characterized his manner as a small child, and resembles a severe disruptive neurosis.

A summary of the possible factors entering into this boy's condition is of interest as indicating the large number of contributing circumstances. From the time of conception, things were against him. Born of a mother in very poor health, with an alcoholic father, he was a frail, sickly child for the first years of his life. Poverty in the home, fear of the drunken father, and the final disruption of the home added further threats to this child who must certainly have been regarded as more vulnerable than average to unfavorable conditions.

At the time of his acute disturbance, there were no facilities available for care and treatment adapted to his needs. Whether he could have profited by such treatment, had it been possible, must remain an open question. He has had kindly care, companionship, and education, probably up to the limits of his capabilities. Beyond this, he has had no special therapy and although docile to the point of being described as "too good," he has no close relations either with the members of his own family or with other boys in the institution. In considering his native ability, so far as it can be estimated accurately, together with his sensitiveness to the threats which ordinary life imposes, it is not unlikely that his present circumstances represent as good a solution to his problems as could be found. Although not happy, he feels safe, and can be sure of protection as long as he lives.

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ABNORMALITIES IN THE SECRETION OF THE ADRENAL CORTEX DURING EARLY LIFE

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AS MORE and more reports appear regarding disturbances in secretion of the adrenal cortex, it becomes increasingly evident that such cases are not rare in children.[1-9] Several clinical types of such disturbance are becoming evident, which include: (1) cases with *hypo*function of the cortex causing Addison's diseases (due to a deficiency in the salt- and water-controlling hormone);[1, 2] (2) cases with *hyper*function of the cortex leading to masculinization and precocious maturation (due to an excess of androgen secretion);[3] and (3) cases which are a combination of (1) and (2) with *excess* of one adrenal hormone, the androgenic, and simultaneous *deficiency* of another, the salt and water controlling hormone.*[4-12]

The purpose of this paper is to add to the ever-increasing evidence that a congenital basis for Addison's disease is not rare, to stress the importance of its recognition in time to be of assistance with replacement therapy, and to present a series of cases demonstrating the pertinent clinical and laboratory findings of childhood Addison's disease and other types of disturbance in adrenal cortical secretion. The following cases are illustrative of some of the types that may be encountered:

CASE REPORTS

SUMMARY OF CASE 1.—J. P. N., a 2½-month-old white male infant, vomited and failed to gain weight, beginning shortly after birth. The vomiting was so pronounced that a Ramstedt pyloroplasty operation was performed but no pylorie hypertrophy was demonstrated. Abnormally low levels of blood sodium and chloride, and an elevated level of potassium, confirmed the clinical diagnosis of Addison's disease. Of particular interest was a 20 per cent eosinophilia on several occasions. Control was achieved with desoxycorticosterone acetate sublingually, aqueous adrenal cortex extract† intramuscularly, and sodium chloride

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*Actually the number of disorders of the adrenal cortex which are possible is much more than just the three types mentioned. When one considers that the disturbances might be unilateral or bilateral; congenital or acquired; neoplastic, hypoplastic, hyperplastic or atrophic; functional or organic; and that they may, in turn, relate to the salt and water function, the carbohydrate function, or the androgenic function of the adrenal glands, the theoretically possible disturbances are obviously very numerous. Actually, however, all combinations of the above have not been described. For a discussion of those which have been recognized clinically, the reader is referred to Lawson Wilkins' article in *Advances in Pediatrics*.[3] Although approximately thirty substances have been isolated from the adrenal cortex, clinically it has been found that many of these substances are inert and that the others act in three principal ways: to control salt and water metabolism, carbohydrate metabolism, and nitrogen metabolism. It has been postulated that all of these functions are under the control of a single hormone, and that the substances isolated in the laboratory are merely chemical artifacts, but this theoretical single hormone has, as yet, not been isolated.

†Eschatin of Parke, Davis & Co., Detroit.

as an addition to the formula. A seemingly satisfactory clinical course was maintained by the subcutaneous implantation of desoxycorticosterone acetate pellets, but at the age of 10 months the patient died after a short stormy illness in spite of having received intensive therapy with various adrenal cortical supplements.

The post-mortem study of the adrenals revealed small islands of a markedly hypoplastic cortex on one side, and complete absence of cortical elements on the other. The kidneys showed vascular changes which may have resulted from overdosage with desoxycorticosterone acetate.[14]

DETAILED CASE REPORT

J. P. N., a 2½-month-old white male infant, was referred to the University of California Hospital in April, 1947, by Drs. J. M. Frawley and N. M. Wolfe of Fresno, Calif., with a history of vomiting and failure to gain weight since birth. The child was born after a full-term normal pregnancy and was delivered by a cesarean section. No abnormality was noted at that time. The birth weight was 7 pounds, 10 ounces (3,460 grams). While still in the nursery he began to vomit excessively, and after leaving the hospital he continued to vomit, loose stools developed, and he went rapidly downhill. When 2 weeks of age, he was seen by Drs. Wolfe and Frawley who found him to be markedly dehydrated and apparently moribund. He was hospitalized, placed in an oxygen tent, given normal saline solution by hypodermoclysis, and a transfusion of whole blood. Thereupon he improved rapidly, retained his formula, and within a few days was sent home. However, in less than a week he had to be readmitted to the hospital since vomiting had resumed and he had again become markedly dehydrated. For the second time he improved temporarily when parenteral fluids were given, but because of renewed vomiting and continued weight loss, a Ramstedt pyloroplasty operation was done. No pyloric hypertrophy was demonstrated. Postoperatively, no great improvement resulted in the condition of the child, and he continued to lose weight. At this time he was referred to us and on admission to the University of California Hospital he weighed 5 pounds, 14 ounces (2,680 grams) compared to the birth weight of 7 pounds, 10 ounces (3,460 grams). He was then 2½ months old.

The mother had had three previous pregnancies; the first two ended in miscarriages at 6 months and 2 months, respectively, for no known specific reason, and the third ended after 8 months with the delivery by cesarean section of a child who died at 3 days of age of "atelectasis." The father had three living, normal children by a previous marriage.

Physical examination revealed a very small dehydrated, cachectic, wheezened infant (Fig. 1*A*). The head showed overriding of the sutures, and the anterior fontanel was depressed. No abnormal skin pigmentation was present. A pronounced loss of subcutaneous fat and poor turgor of all tissues were noted. A healed right rectus scar from the pyloric operation was present on the abdomen. There was some question as to whether the genitalia were slightly enlarged. The head circumference (14⅖ inches, 36.5 cm.) and length (20½ inches, 52 cm.) were those of the average 3- to 4-week-old infant, and below the 1 percentile figures for a 2½-month-old male infant. The blood count was: hemoglobin 16.8 Gm., red blood cells 5.5 millions, white blood cells 25,700, with a differential count of 37 per cent polymorphonuclears of which 5 per cent were nonfilamented, 20 per cent eosinophiles, and 43 per cent lymphocytes.

Shortly after admission, the child was given blood plasma intravenously and glucose solution subcutaneously. On the following day, before the parenteral administration of sodium chloride, the plasma nonprotein nitrogen was 66 mg. per cent and the serum chlorides were 80 meq. per liter (normal 98 to 105 meq. per liter). Saline and glucose solutions now were given intravenously and subcutaneously because of the dehydration and regurgitation. On the third day of hospitalization, the serum chloride value had risen to 95.6 meq. per liter, and the first serum potassium and sodium determinations then made showed 6.6 meq. per

liter (normal 4 to 5 meq. per liter) and 135.0 meq. per liter (normal 138 to 142 meq. per liter), respectively. These low serum chloride and sodium and high potassium levels confirmed our clinical impression of Addison's disease. Regurgitation and vomiting had stopped following the administration of saline solution. On the sixth hospital day, he was started on desoxycorticosterone acetate in the form of Cortate,* three drops (¾ mg.) sublingually six times a day, and aqueous adrenal cortex extract in the form of Eschatin, 1 c.c. intramuscularly, three to six times a day. He also received 1.5 Gm. of sodium chloride daily as an addition to his formula. On this regime the patient improved; he became much more alert, and he gained 450 grams in the following three weeks. During the first few weeks of his hospital stay, the parenteral administration of saline solution was necessary almost daily, but this supplement gradually was decreased and finally could be omitted entirely.

A twenty-four-hour urine specimen during this time contained 0.6 mg. of 17-ketosteroids, a normal value for the method of assay used. The reactions to the Wassermann and tuberculin tests were negative.

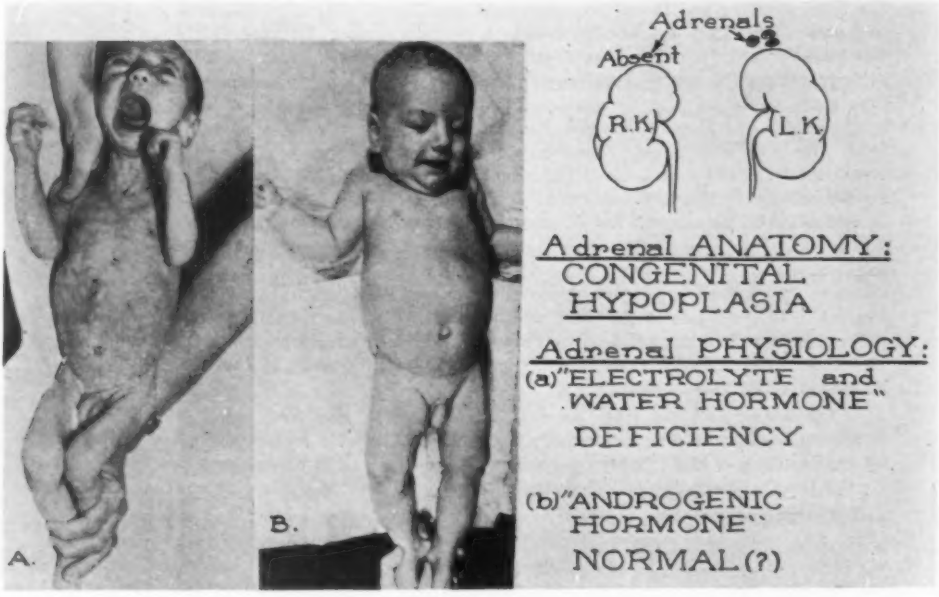

Fig. 1.—Infant (Case 1) with proved congenital hypoplasia of the adrenals. *A*, On admission to the hospital at the age of 2½ months. Note the scar from the operation for suspected congenital pyloric stenosis. *B*, Taken three months after therapy was started, showing the healthy appearance of the child.

One month after admission, the serum sodium was 137 meq. per liter, potassium 6.2 meq. per liter, and chlorides 95.6 meq. per liter, and one month later, just before discharge, the serum potassium value was 5.3 meq. per liter, the chlorides 99 meq. per liter, and the fasting blood sugar 78 mg. per cent. At this time two 75 mg. pellets of desoxycorticosterone were implanted in the subcutaneous tissues of the axilla and the oral and intramuscular administration of that drug was discontinued. He now weighed 9 pounds, 2 ounces (4,140 grams). Although the hemoconcentration had been corrected by adequate hydration during the first few days of treatment, the initial eosinophilia persisted. Six differential counts

*Desoxycorticosterone acetate in propylene glycol 10 mg. per cubic centimeter (Schering Corporation, Bloomfield, N. J.).

during the two months disclosed an eosinophilia of between 17 to 24 per cent, with 15 to 27 thousand white blood cells, and from 33 to 48 per cent lymphocytes.

After discharge from the hospital, the child was seen occasionally at the Out-Patient Clinic and in addition was followed by the referring physicians. At 5½ months of age he weighed 13 pounds (5.9 kg.) and seemed normal physically, save that he was below average in length (Fig. 1*B*). He continued to receive from 6 to 14 drops (1.5 to 3.5 mg.) of Cortate daily and 1.5 Gm. of salt as an addition to his formula. The improvement in his appearance at this stage was truly remarkable (Fig. 1 *B*). Two months later when he was seen again at the age of 7½ months in the clinic, he weighed 16 pounds, 12 ounces (7.6 kg.). His mother had recently increased the dose of Cortate from 8 to 12 drops (2 to 3 mg.) as he seemed "less lively" on the lower dose. During this period he acquired an acute bronchitis and began to vomit. Hospitalization was discussed but improvement occurred after a slight increase in both salt and Cortate to 14 drops daily. Although he appeared well, a slight degree of generalized edema was thought to be present. The serum chloride was elevated (114 meq. per liter), and so the Cortate was reduced to 8 drops daily and the salt supplement to 1.0 Gm. Six weeks later all evidence of edema had cleared and the blood chloride level was normal (98.2 meq. per liter). The mother reported that vomiting again had occurred, this time as an accompaniment of a "cold." On physical examination, the skin was noted to be slightly darkened and it was believed that this possibly was related to the bronzing seen in Addisonian patients. He weighed 17 pounds, 7 ounces (7.9 kg.). The dose of desoxycorticosterone was increased to 12 drops (3 mg.) daily.

Six weeks later the patient died, after a short and stormy period which began with vomiting, diarrhea, fever, reddening of the pharynx, and went on to convulsions and evidence of pulmonary edema. During this time he received intensive therapy with Eschatin, Cortate, and Ringer's solution, Ringer's lactate solution, sodium chloride, and oxygen, but in spite of these he succumbed after a terminal illness of only two days' duration. Post-mortem examination was made in the local community and showed "an acutely dilated heart, especially on the right side, gross evidence of toxic liver changes and no adrenal glands recognizable as such." All tissue in the area normally occupied by the adrenals as well as sections of most of the viscera were sent in formaldehyde solution to the University of California Hospital for further examination. The following is a summary of Dr. R. O. Holmes' report on this autopsy material.

Pathologic Report.—The most striking gross findings were the small size of the left *adrenal gland* which weighed one-half gram and the absence of a recognizable adrenal gland on the right side, although several small white nodules were found in the right subdiaphragmatic area. The *thymus* was enlarged and weighed 45 grams. The kidneys weighed 22.5 and 27 grams., respectively. Microscopically (Fig. 2*A*), the *left adrenal* showed a very narrow cortex about one-third as thick as the medulla which was of normal size and microscopic appearance. The cortical cells were arranged in small groups without a tendency to form the normal zonal pattern. They were large with pale eosinophilic cytoplasm and small nuclei which were frequently pyknotic. Many had pale vacuolated cytoplasm with small eosinophilic droplets between empty spaces. Cells with the appearance of normal adrenal cortical epithelium were present in very small number. Sections of the tissues from the *right adrenal* region showed two separate small masses of medullary tissue with normal cellular components. These nodules were intimately associated with large parasympathetic ganglia and nerve fibers. Multiple sections of the tissues revealed no adrenal cortical elements.

The *kidneys* showed remarkable changes, which were primarily vascular (Fig. 2*B*). The arteries were of normal appearance but the prearterioles and arterioles in all parts of the kidney had lumens which were markedly reduced in size and showed thickening of their walls due to proliferation of smooth muscle and fibroblasts within the media and intima. Hyaline and necrotic changes were not present. Approximately one-fourth of the glomeruli were markedly reduced in size and showed thickening of their walls due to proliferation of smooth muscle and fibroblasts within the media and intima. Hyaline and necrotic

changes were not present. Approximately one-fourth of the glomeruli showed obliterative changes ranging from thrombosis and hyalinization of one of the capillary loops to complete atrophy and fibrosis of the entire structure. In some glomeruli, the cells of Bowman's capsule had proliferated and formed eccentric crescents; in others the entire capsule was thickened. This obliterative process tended to involve adjacent glomeruli with the same vascular supply. Other glomeruli showed no changes save for the presence of a few eosinophiles in many of the capillary tufts. A slight amount of lymphocytic infiltration was associated with the glomerular lesion. In a few instances evidence of early tubular atrophy was noted. A few of the cells of the proximal convoluted tubules had large, clear vacuoles within the cytoplasm. Scattered small calcified bodies were present in a few of the collecting tubules toward the tip of the pyramids.

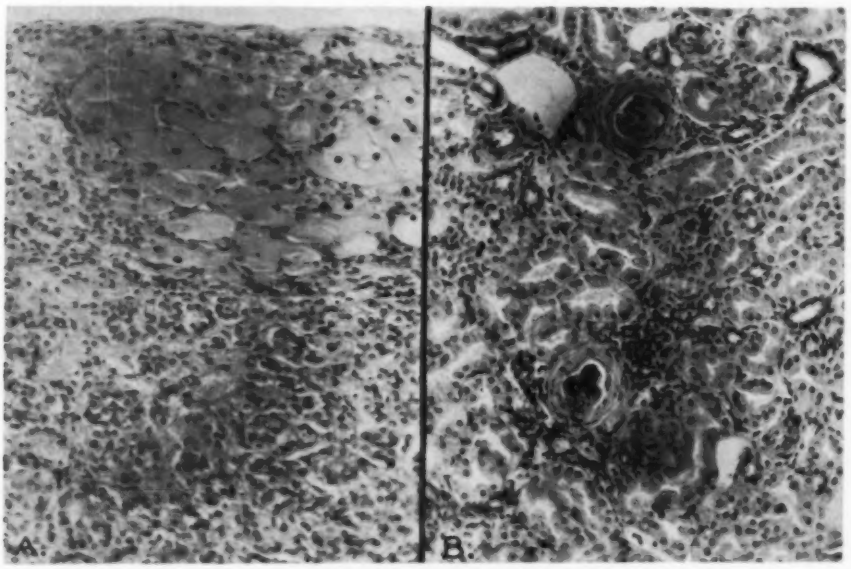

Fig. 2.—*A*, Photomicrograph of the left adrenal of patient (Case 1) showing the thin cortex and the large abnormal cortical cells. *B*, Photomicrograph of the kidney showing obliterative changes of the glomeruli due probably to desoxycorticosterone.

The *lymph nodes* were large and contained unusually large follicles with small germinal centers. Many eosinophiles were present in the sinusoids.

The *thymus* weighed 45 grams and was composed of large tubules with broad cortices made up of closely packed small round cells. The medullar part was not remarkable.

The *heart muscle* was composed of small fibers with well-preserved myofibrils and distinct cross striations. The fibers contained central elongated vesicular nuclei and frequently had small, clear vacuoles in the cytoplasm adjacent to the nuclei. The epicardium, endocardium, and vessels were normal.

The *lung* was partially atelectatic with collapsed alveolar spaces and thickened alveolar walls which formed solid cellular masses in many places. The alveolar spaces contained a few large mononuclear phagocytes in most areas. The bronchioles were collapsed and showed papillary infoldings of the epithelial linings and empty lumens. A few small lymph follicles were seen adjacent to some of the smaller bronchi. There was no evidence of inflammation within the lung or bronchi.

The *liver* was not remarkable save for what appeared to be small discrete fat vacuoles within the cytoplasm of nearly all hepatic cells.

The pathologic diagnosis was: (1) congenital hypoplasia (left) and aplasia (right) of adrenal cortices with (a) hypertrophy of thymus and lymphoid tissue, (b) arteriolonephrosclerosis and obliterative glomerulitis; (2) pulmonary atelectasis; and (3) fatty infiltration of the liver.

SUMMARY OF CASE 2.—J. W. N. had had slow growth, anorexia, regurgitation, occasional vomiting, and increasing lassitude and weakness for the first months of life. The referring doctor elicited the history of poor appetite for everything except salt-containing foods. At the age of 18 months, the patient's blood chemistry was consistent with the diagnosis of adrenal cortical insufficiency, and with adequate replacement therapy his condition improved. At the age of 4 years, although clinically he appeared to be well, the levels of blood sodium, chloride, and potassium were still markedly abnormal and further therapy with pellets of desoxycorticosterone was deemed advisable. Sexual development had been within normal limits, but his growth had been slow.

DETAILED CASE REPORT

J. W. N., a male infant, was first seen by the referring physician, Dr. Charles Mitchell of Fresno, Calif., at 11 months of age with a history of slow growth, anorexia, regurgitation and occasional vomiting, increasing weakness and lassitude. A sibling of 3½ years was normal and there had been no other pregnancies. Although apparently normal at birth, the child gradually became disinterested in food and was difficult to feed. He was delayed in holding his head up and his body growth was slow in comparison with his sister's, but the mother was told by more than one physician not to be concerned. At the age of 6 months, a cough which resembled pertussis developed and continued for several months. The child had not been immunized. When seen at 11 months of age by the referring physician, the child had ceased to crawl and sit up alone, activities which he had begun only a month or so previously. He had gradually become quite weak and there were spells during which he was unable to hold his head up. Feeding difficulty was even more pronounced and was accompanied by vomiting which was not relieved by the administration of atropine. Constipation and dwarfing prompted a trial of thyroid but this did not result in any improvement. Suspecting adrenal cortical deficiency, the physician asked the mother about craving for salt. She said the child's sole interest in food was in salted crackers and potato chips. She had found quite by accident that he liked these two foods and would lick the salt off them. The suspicion of insufficiency having been confirmed to this extent, 2 Gm. of sodium chloride and 1 Gm. of sodium bicarbonate were added to the child's milk and resulted in his immediate acceptance of two quarts of whole milk a day whereas he had previously taken only one pint. Sublingual desoxycorticosterone acetate also was given but only for short periods.

On this regime slight improvement resulted, but was interrupted, first, by an upper respiratory infection and then by diarrhea, the latter causing collapse out of proportion to the degree of diarrhea. At the age of 18 months, shortly after recovery from the diarrhea, he was referred to the University of California Hospital for study. He was then only 27½ inches (69.8 cm.) in length and weighed 13 pounds, 2 ounces (5.96 kg). For purposes of study, the additional salt and soda were omitted from his diet and the patient lost 1 pound, 2 ounces (0.5 kg.) in the next four days. He was thin and scrawny in appearance, listless, inactive, and irritable. Muscle tone was very poor but otherwise the results of the physical examination were negative. No pigmentation of the skin or mucous membranes or abnormality of the genitalia was present. The serum sodium level was found to be 132 meq. per liter, the potassium 4.2 meq. per liter, the blood sugar 121 mg. per cent and nonprotein nitrogen 55 mg. per cent. The white blood count was 17,800 of which 2 per cent were eosinophiles, and the red blood count was 6,100,000. The 17-ketosteroid excretion in the urine was normal (0.6 mg. per twenty-four hours). The reaction to the tuberculin test was negative.

On the basis of these findings a diagnosis of probable adrenal insufficiency was made. On the fifth day in the hospital, he was started on aqueous adrenal cortex extract (Eschatin 5 c.c.) and sublingual desoxycorticosterone acetate (Cortate 18 drops, 4½ mg.) daily, as well as 1.5 Gm. of sodium chloride and 1 Gm. of sodium bicarbonate as additions to the formula. A slow but gradual improvement occurred. Within a week the blood sodium had risen to 139.5 meq. per liter, and the weight from 11 pounds 14 ounces (5.4 kg.) to 13 pounds 7 ounces (6.1 kg.). After three weeks, lipoadrenal extract (1 c.c. intramuscularly daily) was given in place of Eschatin but with no particular change in the child's status. A respiratory infection and otitis media during this time were associated with fever and temporary weight loss.

Six weeks after entry, the serum sodium was 142 meq. per liter, chloride 102.5 meq. per liter, and potassium 3.6 meq. per liter. The child was eating much better, was less irritable, and more active. A psychometric examination gave an I.Q. of only 60 but it was felt the child's physical condition interfered with the determination. During his stay in the hospital, repeated blood counts failed to reveal any eosinophilia. The bone age was at the 10 percentile for his age.

Ten days before discharge, three 75 mg. pellets of desoxycorticosterone acetate were placed in the subcutaneous tissue of the axilla and lipoadrenal extract was discontinued. The child continued to receive 4.5 mg. of Cortate sublingually and 1.5 Gm. of sodium chloride and 1 Gm. of sodium bicarbonate as an addition to the diet. On this regime he showed considerable improvement and in the following ten days he gained two pounds (0.9 kg.).

He was seen in the clinic seven weeks later and had progressed remarkably. His parents felt he was "a different child" from the one they had known. He had gained an additional 3¾ pounds (1.7 kg.), was active, and ate well. Three and one-half months previously, they had brought in a child who did not sit up spontaneously, was disinterested in his surroundings, and very difficult to feed. He now behaved normally, had had a 50 per cent increase in weight, and no longer showed an especial interest in salt.

In the next two months salt, soda, and sublingual Cortate gradually were omitted. He was now 2 years old and had learned to walk. Six months later, the pellets (implanted nine months previously) no longer could be felt. The serum chloride was 106 meq. per liter, and when repeated three months later, it was 101 meq. per liter, with a serum sodium of 139 meq. per liter. His I.Q. now was reported as being 83. He weighed 29 pounds but was only 35 inches tall (89 cm.), which is below the 10 percentile for the age.[13] It was now twenty-two months since the last subcutaneous implantation of a desoxycorticosterone acetate pellet, but the mother reported that he seemed to be entirely well, physically active, and showed no signs of weakness or undue fatigue. The only symptom of note was that he liked his food well salted, although pure salt had been refused by him on numerous occasions.

Physical examination at that time showed the child to be normal, except for the short stature. There was no abnormal pigmentation of skin or mucous membranes and the genital development was normal. However, check-up of his blood electrolytes revealed a serum sodium of 135 meq. per liter, and a serum chloride of 93.5 meq. per liter. The 17-ketosteroid assay on a twenty-four-hour urine specimen was 0.9 mg.

Because of the abnormally low serum chloride and serum sodium, he was readmitted to the hospital for study on Dec. 6, 1949. He continued to show some polydipsia, polyuria, and urinary frequency which had been present for many months, but the urinalysis gave normal results with a high specific gravity following a period of fluid restrictions. It was reported that within the preceding few months he had had two earaches, an episode of Vincent's angina, measles with a sustained temperature of 102° F., but that he had had no particular difficulty with any of these illnesses. (Fig. 3*A*.)

Blood chemistry revealed a sodium of 132 meq. per liter, serum chloride 94.8 meq. per liter, potassium 5.6 meq. per liter, cholesterol 210 mg. per cent, protein bound iodine 4.2 units, CO_2 45 vol. per cent, and nonprotein nitrogen 39 mg. per cent. The I.Q. at this time was 96. Roentgenograms of the abdomen revealed no abnormal calcification in the region of the adrenal glands.

Because of the abnormally low serum sodium and chloride, a 75 mg. pellet of desoxycorticosterone acetate was again implanted in the subcutaneous tissues of the axilla. This was

done in order that he might have an additional reserve in a time of emergency even though he was experiencing no unusual clinical symptoms at the time.

When last seen in the Endocrine Clinic, in February, 1950, his condition continued to be good. The serum sodium was 136 meq. per liter, serum chloride 104 meq. per liter, and serum potassium 5 meq. per liter.

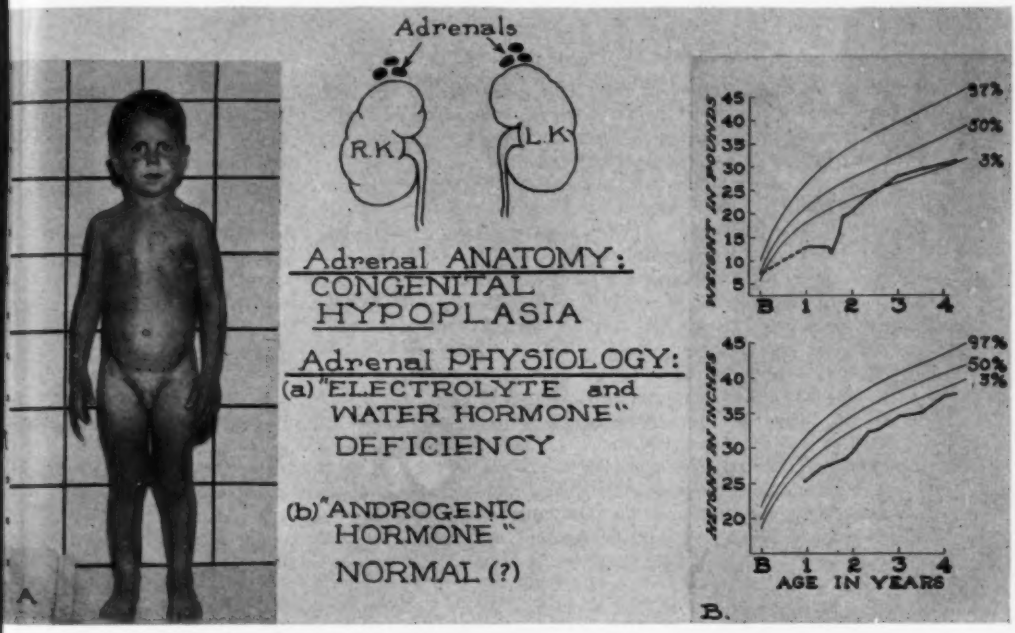

Fig. 3.—Child (Case 2) with probable congenital hypoplasia of the adrenals. *A*, At the age of 3½ years, showing the healthy appearance of the child after two years of replacement therapy. *B*, Height and weight graph of the patient. The percentiles used are taken from Stuart and Stevenson.[13]

SUMMARY OF CASE 3.—J. M., a 2½-month-old boy began to vomit excessively and projectilely in the second week of life. When hospitalized and given normal saline by hypodermoclysis, there was moderate improvement, but when supportive measures were discontinued, vomiting recurred. A diagnosis of pyloric stenosis was entertained for a time. Laboratory data were consistent with the diagnosis of adrenal cortical insufficiency and control was achieved with adequate replacement therapy.

Initially it was noted that the penis seemed abnormally large and excessive androgen secretion by the adrenals was proved by the finding of an abnormally high level of 17-ketosteroids in the urine, as well as by the development of clinical evidences of precocious sexual development.

Replacement therapy with desoxycorticosterone acetate was necessary until the age of 5 years when it was found that it could be discontinued. Excessive growth of stature and advanced epiphyseal development continued during the

next two years, although no supplemental therapy for the adrenal cortical insufficiency had been necessary. It would appear that after manifesting a need for replacement therapy for the first 5 years of his life, he had reached a state of equilibrium where his own adrenal glands were able to supply an adequate amount of the salt and water metabolic fraction under ordinary conditions but not under conditions of stress. There was still evidence of excessive androgen production (Fig. 5).

DETAILED CASE REPORT

J. M. was born on April 22, 1943. He weighed 7½ pounds (3,410 grams) at birth, and during the first week he did well except for slight regurgitation. Vomiting then began and increased in frequency and occasionally was projectile. At the age of 2 weeks, he was hospitalized at Children's Hospital in Oakland, Calif., with a tentative diagnosis of pyloric stenosis. On entry he was markedly dehydrated, and typical gastric waves were seen but no pyloric tumor was felt. A gastrointestinal study with barium by mouth failed to reveal any abnormal gastric retention. He was given normal saline solution by hypodermoclysis and whole blood transfusions, and there was some improvement in his clinical condition. However, when supportive measures were discontinued, vomiting recurred. After a few weeks, gastric peristaltic waves again were noted and a second barium study was done which also gave negative results. During this hospital stay, otitis media had occurred and weight gain was very poor. He was transferred to the University of California Hospital, at the age of 2½ months, weighing only 6 pounds, 12 ounces (3,060 grams). There was no family history of a similar condition in any sibling.

On entry he was inactive, poorly nourished and dehydrated (Fig. 4*A*). Tissue turgor was poor and the anterior fontanel was depressed. The penis was noted to be large. The remainder of the physical examination was not remarkable. A blood count showed 5,200,000 red blood cells, 15 Gm. of hemoglobin, and 29,200 white blood cells with 12 per cent eosinophiles. The reaction to the tuberculin test was negative. A clysis of Ringer's solution was given on the day of entry but by the third day the weight had dropped to 5 pounds 14 ounces (2,660 grams). Because of the persistent dehydration, the possibility of Addisonian deficiency was considered, and serum sodium and chloride determinations were made. These were 126 meq. per liter, and 77.1 meq. per liter, respectively—low values which were consistent with a diagnosis of Addison's disease. The nonprotein nitrogen was 54 mg. per cent. Daily administration of clysis of normal saline solution and 5 to 8 c.c. of aqueous adrenal cortex extract (Eschatin) intramuscularly then were started and 2.0 Gm. of salt were added to the formula each day. This therapy brought about a marked improvement in the baby's condition and appearance during the ensuing weeks. However, consistent and satisfactory weight gain was not maintained until the dose of adrenal cortex extract had been increased to 24 c.c. daily and desoxycorticosterone acetate (Cortate) was added in amounts of from 10 to 24 drops daily, with the dietary salt being somewhat reduced. After a month on this program, the dose of adrenal cortex extract gradually was reduced and finally was omitted entirely, and the child was discharged from the hospital. He had gained two pounds (0.9 kg.) during the last month and a total of 6 pounds, 1 ounce (2,730 grams) during the six weeks he was in the hospital. The serum sodium had risen to 134 meq. per liter. He was given 32 drops of desoxycorticosterone acetate sublingually daily at home and a "pinch" of salt was added to each bottle. From this point on, progress was satisfactory (Fig. 4*B*) and the desoxycorticosterone gradually was reduced to 8 drops (2 mg.) daily.

The patient's advancement of bone age and precocious sexual maturation gradually manifested themselves during the second year. At the age of 16 months, the urinary 17-ketosteroids were 5.9 mg. per twenty-four hours, and the bone age (which had been equal to his chronological age at 11 months) was advanced to that of the normal 2½-year-old child. The intelligence quotient, estimated as 80 during hospitalization, was 106. In order to determine the need for replacement therapy, the patient was hospitalized and the desoxycorticosterone was discontinued. Within three days he lost 1 pound, 5 ounces (600 grams),

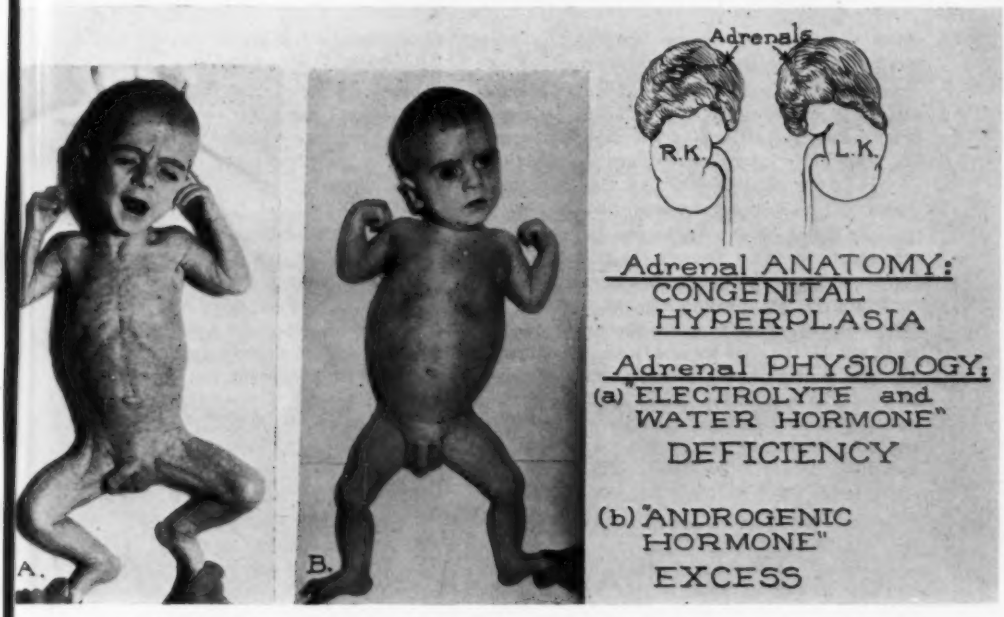

Fig. 4.—Infant (Case 3) with congenital hyperplasia of the adrenals. *A*, On admission to the hospital at the age of 2½ months. Note the wizened appearance, sunken eyes, and slightly enlarged penis. *B*, Taken two months later showing the adequate nutrition and healthy appearance of the child.

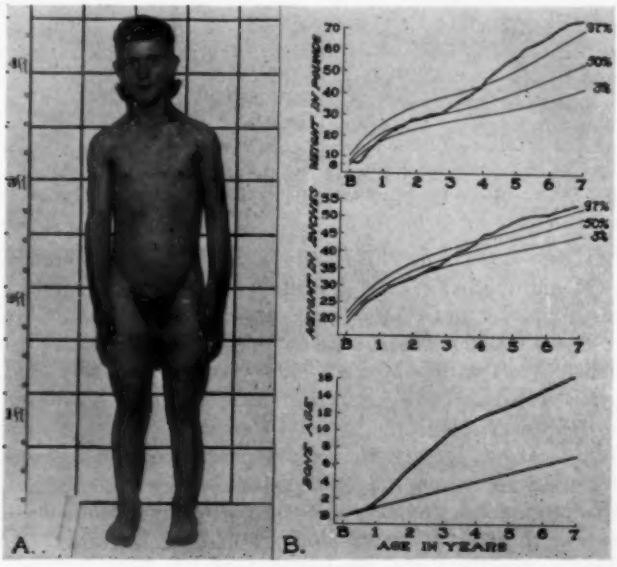

Fig. 5.—*A*, Child (Case 3) at the age of 6 years, 10 months, showing the evidences of precocious physical and sexual development. *B*, Height, weight, and bone age graphs. Note the normal linear growth until the third year of life and the normal maturation of the epiphyseal centers for the first eleven months of life.

began to vomit, and became dehydrated. Resumption of desoxycorticosterone therapy and saline clysis promptly relieved these symptoms.

In the next year he continued to do well on small doses of sublingual desoxycorticosterone acetate (3 or 4 drops a day) although he manifested a moderate desire for extra salt and became limp and listless on hot days if the medication was not increased. At the age of 2½ years pubic hairs appeared, and it was quite evident that growth was faster than normal. The 17-ketosteroid level was 14.9 mg. in a twenty-four-hour urine specimen. When he was 3 years old his bone age was equivalent to that of a 10-year-old child.

At the age of 4 years he was 44 inches (112 cm.) tall, and his intelligence quotient was reported to be 134. Acne of the face was present. When he was 4½, a 75 mg. pellet of desoxycorticosterone acetate was placed under the skin in the axillary area and oral desoxycorticosterone was discontinued. At this time the voice was deep, and the penis was 10 cm. long with the testes being the size of a prepubertal youth. When 5½ years old, the pellet could not be felt, but blood sodium, potassium, and chlorides were at average normal levels. The results of a glucose tolerance test also were normal. The first permanent tooth appeared at about the age of 5½ years. In June, 1949, at the age of 6 years, 2 months, he was 52 inches (132 cm.) tall (average for 9 years). It had been nineteen months since the pellet had been implanted, and we felt that it had been almost a year since it had been completely absorbed. However, his serum sodium was 139 meq. per liter, potassium 4.1 meq. per liter, and chloride 100.5 meq. per liter. No abnormal pigmentation of the skin was present, and he did not fatigue easily. He preferred playing with older children, but no behavior problems were evident.

During the summer of 1949 he visited Kansas. It was exceedingly hot there at the time and both he and his sister had a diarrhea which lasted for three days. The mother gave the patient one 2 mg. desoxycorticosterone acetate tablet (Linguet*) daily for three days, and after that time, both he and his sister were well. The mother was not certain that he had needed replacement therapy at the time, but had been told to give him the medication should such a condition as diarrhea arise.

He was last seen in July, 1950, at the age of 7 years, 3 months. He weighed 79¾ pounds (36.25 kg.) and was 53.9 inches (137 cm.) tall. It was two and one-half years since the last pellet had been implanted. He was feeling fine and appeared not to require supplemental desoxycorticosterone. However, in May, 1950, he had required supplemental medication when he acquired a severe pharyngitis associated with vomiting and a fall of blood sodium to 134 meq. per liter. He would occasionally take plain sodium chloride in addition to what was placed in his food. On physical examination he now had a slight amount of axillary hair (which had developed within the past six months). His dental age was between 7 and 8 years. There was some acne of the back, and his voice was becoming progressively deeper.

SUMMARY OF CASE 4.—A. I. B., a 3-week-old infant was first seen for the purpose of determining her sex. Following a complete study, it was concluded that she was a female who showed evidence of excessive masculinization and that she also had Addison's disease. Effective control of the latter was achieved, but the precocious sexual development along heterosexual lines continued and was accompanied by excessive growth, advanced bone age, and increased excretion of 17-ketosteroids in the urine. Attempts to withdraw desoxycorticosterone acetate from her therapeutic regime always resulted in the appearance of signs of insufficiency. At a later time an episode of infectious diarrhea with vomiting precipitated an adrenal crisis. Of particular interest was the history of excessive vomiting in a younger sibling who had died on the day she was scheduled for an operation for a presumed pyloric stenosis.

*Ciba Pharmaceutical Products Incorporated, Summit, N. J.

DETAILED CASE REPORT

A. I. B., a 3-week-old infant, was admitted to the University of California Hospital on Jan. 16, 1947, for the purpose of determining her sex. At birth, the labia majora had been enlarged and wrinkled, and had resembled a bifid scrotum with the phallus resembling a penis with a marked hypospadius (Fig. 6).

Study of the patient from the standpoint of determination of the sex was interrupted by progressive feeding difficulty, vomiting, and marked weight loss, all of which had begun two days before entry. A week after entry the child weighed 8 pounds, 10 ounces (3,910 grams), having weighed 10 pounds, 4 ounces (4,680 grams) at birth. A tentative diagnosis of pyloric stenosis was made by the intern, and when the parents were informed they expressed particular concern since they had lost a child a few years previously when he also had begun to vomit at 3 weeks of age and had died after an illness lasting several weeks, on the day he was scheduled for operation for a presumed pyloric stenosis. This sibling had had normal male genitalia.

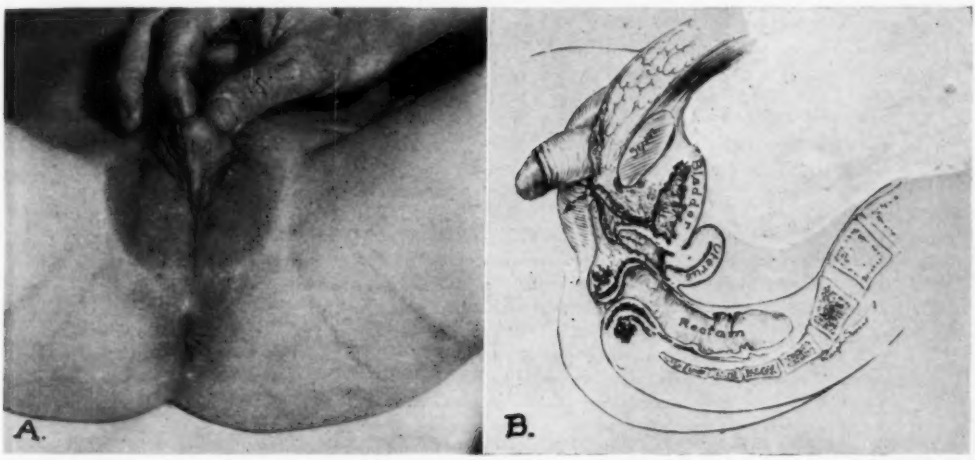

Fig. 6.—*A*, Photograph (Case 4) of the genitalia of a patient at the age of 2½ years, showing the pubic hair and pseudohermaphroditism. *B*, Diagrammatic representation of the anatomic findings.

It now became apparent that we were dealing with a female pseudohermaphrodite who had undergone masculinizing influences from hyperplasia of the adrenal cortex in utero and who was developing an Addisonian type of deficiency under our eyes, and that the sibling may have died of Addison's disease. This diagnosis was confirmed in our patient by the low blood chloride and sodium levels (86 and 130 meq. per liter, respectively) as well as by subsequent improvement on added dietary salt, normal saline by hyperdermoclysis, and the sublingual administration of 20 drops (5 mg.) of desoxycorticosterone acetate daily. There was, however, a difficult period of a week before stabilization of electrolytes and an adequate fluid balance was reached. During this time a urinary tract infection was present, which had undoubtedly been aggravated by repeated catheterizations.

Pneumovaginograms and vaginoscopy through the common opening of the vagina and urethra (urogenital sinus) revealed a normal-sized vagina and cervix (Fig. 6). A twenty-four-hour urine specimen showed a marked increase in androgens (16 mg. of 17-ketosteroids). On entry, hemoconcentration was reflected by a red blood count of 7,600,000, and a hemoglobin of 22 Gm. The white blood count was 14,250 with 6 per cent eosinophiles. Three weeks after entry the patient was discharged, weighing 10½ pounds (4,760 grams).

During the following ten weeks the infant did well when therapy included the daily administration of 10 drops of desoxycorticosterone acetate sublingually along with 1 Gm. of sodium chloride and 0.5 Gm. of sodium bicarbonate as an addition to the daily formula. When the mother attempted to omit the desoxycorticosterone, the infant began to vomit and became restless.

The family then moved to Oklahoma City and the patient was not seen again until October, 1948, sixteen months later, when she was 22 months old. The parents reported that she had developed pubic hair at 9 months. The phallus had enlarged considerably, and an abnormally rapid rate of body growth was present. During her absence, she had been given between 6 and 16 drops (1.5 and 4 mg.) of desoxycorticosterone acetate daily, and had received additional salt and sodium bicarbonate in her diet. Attempts to withdraw the desoxycorticosterone had resulted in "fussiness, restlessness, and a facial rash," which were immediately relieved by resumption of treatment with the medication. At times she would lick salt from her palm.

On her return to San Francisco, determination of serum electrolytes showed them to be within normal limits (chloride 103 meq. per liter, sodium 142 meq. per liter, and potassium 4 meq. per liter). The urinary 17-ketosteroid excretion was still markedly elevated. A 75 mg. pellet of desoxycorticosterone acetate was implanted in the subcutaneous tissues of the axilla in October, 1948, and a second one in January, 1949, when it seemed absorption from the first was inadequate. At the time the second pellet was implanted, the patient was hospitalized and a laparotomy was performed. Normal tubes, ovaries, and a small uterus were found, and biopsy of one ovary showed normal infant ovarian structure. During the period of hospitalization, before the pellet was implanted, it was noted that the child was not responding satisfactorily to the sublingual dose of desoxycorticosterone acetate which, it had been thought, would be adequate. On investigation it was found that refrigeration of the medication had resulted in crystallization of its active principle so that the child mainly had been receiving the solvent with insufficient desoxycorticosterone. This deficiency of oral therapy resulted in vomiting and loss of weight. On this occasion an eosinophilia of 10 per cent was noted. The intelligence quotient was 104 and the bone age was consistent with a chronological age of 7 years, although the patient was only 2 years, 1 month old. With the implantation of the second pellet, oral desoxycorticosterone was not needed until July, 1949, when "marked fussiness and restlessness and a facial rash" as well as increased demand for salt again indicated the need for more desoxycorticosterone. A third 75 mg. pellet was implanted seven months following the implantation of the second one, and the parents reported that four days after the pellet had been inserted, she became less fussy and had a better disposition, although she continued to want extra salt occasionally. They said that the "musty smell" of the scalp, which had been present when she was in poor control, had disappeared. Although we were unable to identify this odor, the parents had noticed it on several occasions when she was in poor control and had stated that the odor disappeared when the clinical condition improved and the disturbed blood chemistry returned to normal. The eosinophilia reached 15 per cent in July, 1949.

In the preceding months, the family had discussed the prospect of having to contend with continued masculinization of the child with its accompanying development of a very muscular body build, facial hair, and deepening of the voice. They decided it would be better to rear the child as a male, and changed her name to Alan. In boy's clothes, with short hair, Alan looked more like a boy than Anita had looked like a girl.

In August, 1949, he was readmitted to the hospital for the first stage of a urethroplasty. On the day after entry he began to vomit, was listless, and apathetic. The serum chlorides were then 93 meq. per liter, and serum sodium 128 meq. per liter. He was given 1,000 c.c. of isotonic saline intravenously, and desoxycorticosterone acetate sublingually, and responded well. By the following day the serum chloride rose to 102 meq. per liter. The blood pressure was 104/66.

On Sept. 1, 1949, the first stage of a hypospadius repair was performed under ether anesthesia. The patient withstood the operation quite well and the postoperative course was uneventful.

He was seen in the clinic at periodic intervals and continued to do quite well (Fig. 7*A*). When seen in March, 1950, at the age of 3 years, 2 months, he weighed 55¼ pounds (25.1 kg.) and was 46½ inches tall (118.3 cm.). He was receiving 1 to 1.5 Gm. of salt daily as an addition to the diet, and had needed supplemental desoxycorticosterone acetate by mouth only when he had had an episode of epidemic diarrhea and vomiting. His general condition was good, and his serum sodium was 136 meq. per liter, serum potassium 4.5 meq. per liter, and serum chloride 110 meq. per liter. Three weeks later, hospitalization became necessary for a severe Salmonella diarrhea. An adrenal crisis developed rapidly in the patient and required intensive therapy with intravenous normal saline and glucose solutions, as well as lipoid and aqueous adrenal cortex extract and cortisone. Under this regime prompt improvement occurred.

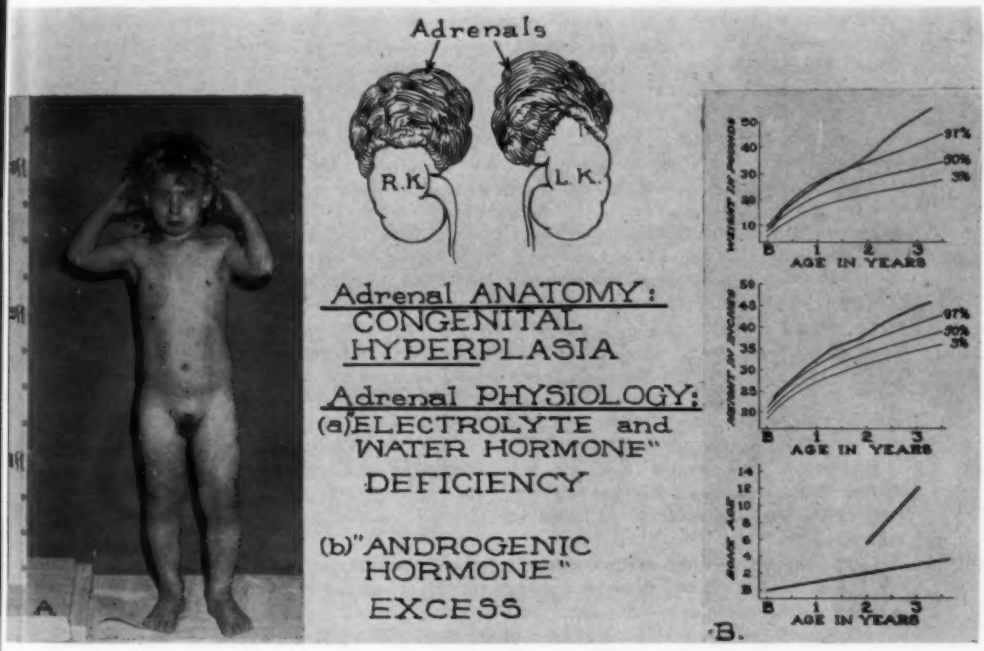

Fig. 7.—Female infant (Case 4) with congenital bilateral hyperplasia of the adrenals associated with Addison's disease. *A*, At the age of 3 years. Note the muscular build, the pubic hair, and the penislike phallus. *B*, Height, weight, and bone age graphs showing precocious development.

SUMMARY OF CASE 5.—W. K., as in the preceding case, is also a pseudohermaphrodite in whom marked dehydration, vomiting, and weight loss occurred in the first week of life. There also had been an older sibling who had died at the age of 4 months of adrenal insufficiency and who was a pseudohermaphrodite. Control of the patient's adrenal insufficiency was achieved with desoxycorticosterone acetate sublingually and later by pellet implantation. A complete study

revealed that, although thought to be a male at birth, she was a female who had undergone excessive masculinization. The child has been observed for over three years and has continued to show a need for replacement therapy. Premature sexual development along masculine lines has been marked, and the bony age has become increasingly more advanced. An attempt at surgical repair of the "hypospadius" was complicated by a severe adrenal crisis which was controlled by the use of large doses of adrenocortical extract.

DETAILED CASE REPORT

W. K. was referred to the University of California Hospital at 6 weeks of age by Dr. Milton Kurzrok of the U. S. Naval Hospital, Oakland, Calif. At birth, the genitalia had been similar to those of the preceding case with labia resembling a scrotum, a greatly enlarged clitoris which resembled a penis with hypospadius, and a urogenital sinus. The infant was mistakenly thought to be a male by both the obstetrician and the genitourinary consultant. A sibling had died several years previously at the age of 4 months, after an illness associated with vomiting and dehydration. This sibling was believed to have died of adrenal insufficiency and had been considered a female although the appearance of the genitalia was identical with that of our patient. The patient also had one normal sister who was two years older.

For the first few days of life the infant appeared well, but then vomiting, dehydration, and marked loss of weight occurred, necessitating admission to Dr. Kurzrok's service at the Naval Hospital. Here the child improved and ceased to vomit when a daily clysis of normal saline solution was given but dehydration persisted, and adrenal insufficiency was suspected. The child was given adrenal cortex extract and 1 Gm. of sodium chloride parenterally for several days, and was then referred to the University of California Hospital. Here the blood sodium and chloride levels were found to be slightly low (137 and 94 meq. per liter, respectively) and the blood potassium level elevated (5.4 meq. per liter). These findings were all consistent with an Addisonian type of adrenal cortical deficiency. Small doses of aqueous adrenal extract (Eschatin) were given and salt was added to the diet. This caused some, but not much, improvement. When desoxycorticosterone was given (4 drops of Cortate every 4 hours sublingually), there was considerable improvement and a gain in weight. Vaginograms and endoscopy revealed a normal vagina and cervix beyond a urogenital sinus. Since no testes were evident, it was felt that the child was a female. The 17-ketosteroids were elevated to 4.1 mg. in a twenty-four-hour specimen of urine. Whereas the initial red blood count had been 4,200,000, the count after hydration was 3,800,000. No eosinophiles were reported in the blood count. The reaction to the tuberculin test was negative.

The parents were informed of the sex of the infant but they decided to continue rearing her as a boy. Therefore we will (inaccurately) subsequently refer to this patient as "he."

In the following months the child did well when given 6 to 9 drops of desoxycorticosterone daily under the tongue, with supplementary salt in the diet. After six months an unsuccessful attempt was made to reduce the amount of the desoxycorticosterone but it resulted in listlessness, vomiting, and fever. A pellet of 120 mg. of desoxycorticosterone acetate then was implanted in the subcutaneous tissue of the axilla. The child's condition seemed to be better controlled with the pellet than it had been with the sublingual medication, and it remained palpable for eight months at which time the need for additional replacement therapy manifested itself in the form of vomiting and weight loss. In May, 1948, a second pellet (75 mg.) was implanted, and shortly therafter sublingual desoxycorticosterone was discontinued.

During the first year there had been only slight evidence of abnormally rapid growth and advancement of the bone age, the latter being approximately at the 1-year level when the patient was 8 months old. However, by the time the patient was 2 years old, the bone

age was at the 7-year level, and 4.8 mg. of 17-ketosteroids were found in the twenty-four-hour urine specimen. The intelligence quotient was 107. At 28 months of age, the second pellet no longer was palpable and during the following month signs of cortical deficiency (vomiting, increased desire for salt, and weight loss) appeared. The blood chloride and sodium levels again were found to be low (96 and 130 meq. per liter, respectively). The third pellet of 75 mg. then was implanted, just twelve months after the second one.

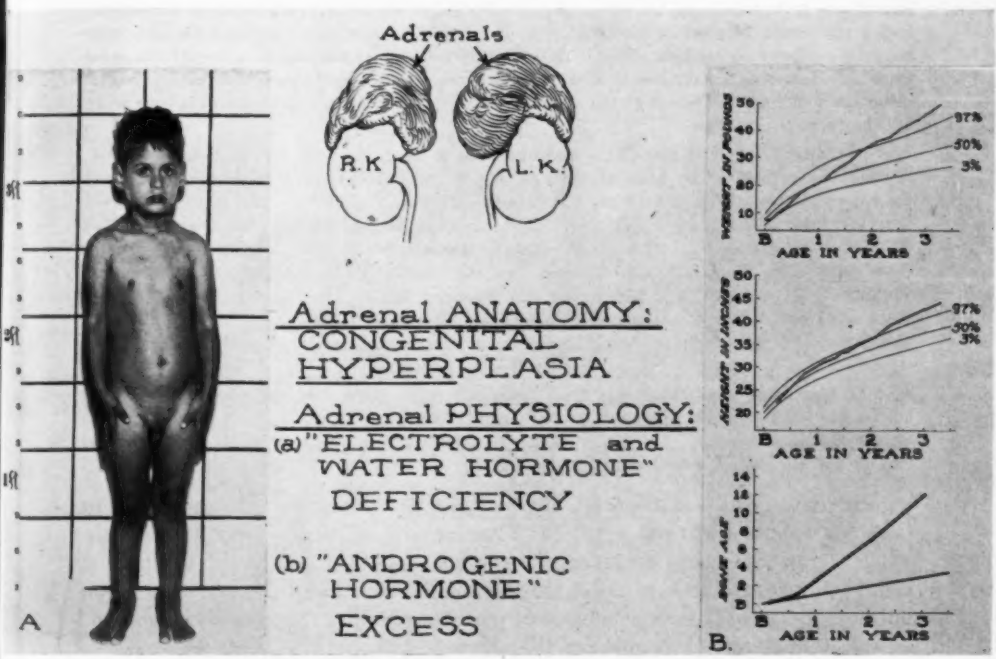

Fig. 8.—Another female infant (Case 5) with congenital bilateral hyperplasia of the adrenals with associated Addison's disease. *A*, At the age of 2 years, 10 months. *B*, Height, weight, and bone age graphs.

In October, 1949, at the age of 2 years, 10 months (Fig. 8*A*), he was readmitted to the hospital for a plastic repair of the hypospadius and for release of the chordae. At that time his serum sodium was 141 meq. per liter, and the serum chloride 105 meq. per liter. A modified Wehrlbein operation was attempted, but following repair of the chordae, a marked drop in blood pressure occurred, the child became apneic and had a tremor of the jaw, and twitching and hypertonicity of the extremities. He was given artificial respiration, Lipo-Adrenal Cortex extract (Upjohn), and an intravenous infusion of 5 per cent glucose and saline. He was returned to the ward in poor condition and during the afternoon his temperature rose to 104.2° F. It was believed that this might have resulted from the intravenous injection of glucose solution.* An electrocardiogram was normal, without evidence of potassium effect. On the following morning, his condition continued to be poor. The blood sodium was down to 130 meq. per liter, with a serum chloride of 91.6 meq. per liter. He was given 2 c.c. of Lipo-Adrenal Cortex extract intramuscularly every four hours, as well as normal saline solution by slow intravenous drip. To this, 25 c.c. of aqueous adrenal cortical extract

*Thorne and Forsham have found that adults with Addison's disease will readily run a fever following intravenous injection of glucose.

were added. This therapy was continued during the course of the day. After being in a critical condition for a few days, there was gradual improvement and return of the blood chemistry to normal. On the fifth postoperative day his blood pressure rose to 140/90 and it was believed that this might have been the result of overtreatment with saline and adrenal extract. However, within the next twenty-four hours, the blood pressure returned to normal and remained there throughout the remainder of the hospital stay. In the five days immediately following surgery, he received a total of 120 c.c. of aqueous adrenocortical extract, and 40 c.c. of Lipo-Adrenal Cortex extract in addition to the fluids given intravenously and by hypodermocylsis. Just before discharge from the hospital, a cytological examination of a vaginal smear showed no estrogen effect. The pituitary gonadotropin assay on a twenty-four-hour urine specimen was negative at 5 mouse units. It is interesting to note that this patient's blood eosinophilia rose from 0 at the start of this hospital entry to 6 per cent at a time when he was in poor condition.

He was followed in the Clinic and appeared to be doing well, but in February, 1950, he was readmitted to the hospital with an upper respiratory infection, otitis media, and vomiting of several days' duration. His temperature was 102° F. The mother reported that the demand for supplemental salt had increased during the previous week and that she had been giving him 2 drops of desoxycorticosterone acetate (Cortate) sublingually twice daily since the vomiting had begun. In the hospital he was given 4 c.c. of aqueous adrenocortical extract (Upjohn) immediately on entry, and 3 c.c. every six hours for two doses. He also received intramuscular penicillin. He made a speedy recovery, and before discharge a 75 mg. pellet of desoxycorticosterone was again implanted in the left axillary region.

It was noted that there was some increased pigmentation of the gums, but it could not be determined whether this was due to adrenal insufficiency or whether it was the result of the racial background, his mother being an American Indian. He was now 3 years, 3 months old, weighed 47 pounds (21.4 kg.) and was 44¼ inches (112.5 cm.) tall.

SUMMARY OF CASE 6.—N. P. is a girl now 4½ years old, who was noted to have an enlarged clitoris at birth. Excessive androgen secretion was subsequently manifested by an elevated excretion of 17-ketosteroids, advanced bone age, rapid growth, and the appearance of pubic hair before the age of 3 years, but no evidence of adrenal insufficiency was ever present. The sex of the patient, as well as bilateral enlargement of the adrenals, was proved by laparotomy.

DETAILED CASE REPORT

N. P., an 8-month-old white female, was referred to one of us by Dr. H. E. Long, of Berkeley, because of abnormality of the genitalia. The birth, early development, and weight gain had been normal; however, a markedly enlarged clitoris had been noted at birth, which the mother did not believe had become any larger although it had continued to be of abnormal size. There had been no symptoms suggestive of adrenal insufficiency. She weighed 18 pounds, 9 ounces (8,420 grams) and was 27½ inches (70 cm.) tall. None of the teeth had erupted. On physical examination, the child looked like a normal 8-month-old girl save that examination of the genitalia revealed an enlarged clitoris, with the bladder opening at the base of this phallus and the vagina leading up to a uterus. The remainder of the physical examination was within normal limits.

The complete blood count was within normal limits, with only 3 per cent eosinophiles. The 17-ketosteroid level of the urine was 4.9 mg. (ketonic fraction).

She was examined by Dr. Frederick Howard of the Genito-Urinary Division, who found a urogenital sinus, into which the bladder opened. There was also a small opening into what was probably the vagina but this latter was too small to admit the endoscope so the cervix was not visualized. However, radiopaque material was inserted into the opening and the roentgenograms visualized a cavity whose configuration suggested a vagina.

No prostate gland was palpated. Although the length at the time was normal, rapid growth and further masculinization were predicted because of the high androgen content of the urine.

In May, 1948, at the age of 2 years, 7 months, the 17-ketosteroids were found to be 6.6 mg. per twenty-four hours.

She re-entered the hospital in September, 1948, at the age of 34 months, and there still was no evidence of adrenal insufficiency. The findings of the physical examination were essentially as before, except that a few long black pubic hairs were now present and there were some blackhead precursors of acne. She was 39½ inches (100.4 cm.) tall, and looked and acted like a very tall normal 3-year-old female (Fig. 9). The bone age was reported as being between 9 and 10 years. The reactions to the Wassermann and tuberculin tests were negative. No eosinophilia was found in the peripheral blood.

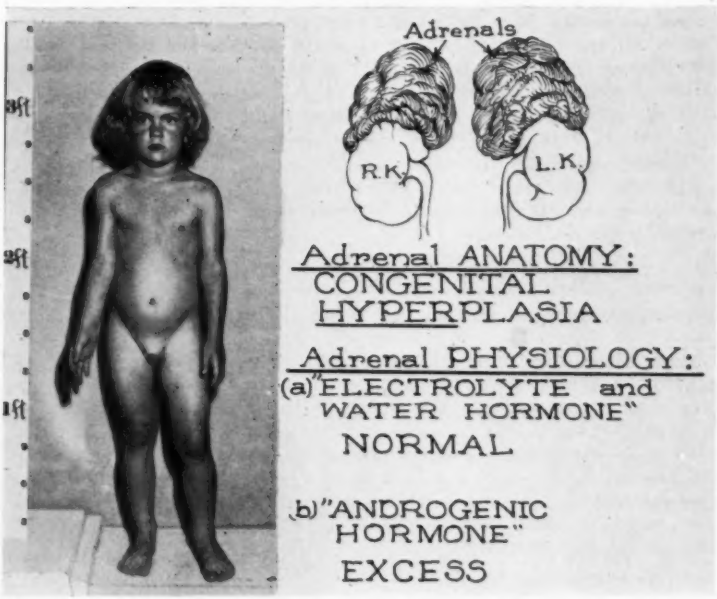

Fig. 9.—A female child (Case 6) with congenital bilateral hyperplasia of the adrenals but without Addison's disease.

Because of the possibility of an aberrant testicle being present, and in order to determine definitely the sex of the child, exploratory laparotomy was carried out on Oct. 4, 1948. The uterus appeared to be normal for a child of 3 years. The ovaries were moderately cystic and the surface was studded with numerous clear cysts which had the appearance of follicle cysts. No testicular tissue was found. Biopsies of the ovaries were reported as showing normal infantile ovarian tissue. Both adrenal glands were investigated and were felt to be diffusely enlarged, although they had a normal configuration. The clitoris, which was between 3 and 3½ inches (7.5 to 8.75 cm.) long, was removed and an appendectomy performed. On microscopic study, the clitoris was normal except for being hypertrophied. In October, 1949, maturation of the skeletal structure was between 10 an 12 years, according to the Englebach and Shelton prediction tables, although the child was then only 3 years, 11 months old.

SUMMARY OF CASE 7.—An. B. first developed precocious sexual characteristics at the age of 2 years. These included progressive enlargement of the genitalia, increased height and muscular development, and pubic, axillary, and facial hair. He entered the hospital at the age of 6 years in an acute Addisonian crisis, and with severe abdominal pain, tenderness, and distention. He was comatose and in shock. The adrenal crisis was controlled and a large abdominal mass was removed and found to be an adrenal adenoma. After a stormy course, he recovered and has gone on to early arrest of his rapid growth without further Addisonian episodes.

DETAILED CASE REPORT

An. B.,* male, first entered the University of California Hospital in May, 1941, at the age of 6 years, 4 months. Since the age of 2 years, precocious sexual characteristics had been noted, which included progressive enlargement of the genitalia and pubic and axillary hair. Hair on the upper lip and acne had appeared at the age of 3 years. Nocturnal emissions had started when he was about 5 years old. Approximately six months before entry, he suffered a twelve-hour attack of pain in the right upper abdomen, and had passed some red urine. On the day prior to entry, similar symptoms had recurred, in the following sequence: fever, abdominal distention, pain, rigidity, and then the appearance of a mass in the right upper quadrant. Within twelve hours the boy was stuperous and delirious. The past history was otherwise normal. Eruption of his permanent teeth or shedding of deciduous teeth was not known.

Family history revealed that there had been one maternal cousin who was precociously developed, from unknown causes, and who died at the age of 13 years of meningitis.

Physical Examination.—Although only 6 years, 4 months old, the child had the sexual development and characteristics of a 16-year-old boy (Fig. 10*A*). He was very muscular and his height corresponded to the average of 12½ years. Acne was quite marked on the face and chest. The voice was very deep. The heavy axillary and pubic hirsutism was accompanied by downy growth on lip and chin, and profuse growth on arms and legs. The denture was that of 12 years. The size of the penis, scrotum, and testes was like those of an average boy of 16 years. Subsequently, a normal prostatic secretion, but no sperm, was found. The abdomen was distended, rigid, and quite tender, especially in the right upper quadrant, where a large mass vaguely could be felt under an enlarged liver. The boy was semicomatose, his color ashen gray, the skin cold and moist, pulse 80, temperature subnormal, respirations 20, and blood pressure 120/70.

Laboratory Findings.—Blood: hemoglobin 13 Gm., red blood count 4,650,000, white blood count 16,450 with 85 per cent polymorphonuclears. The urine contained albumin and many red cells. The blood sugar was 162 mg. per cent. An intravenous pyelogram showed a deformity of the upper portion and displacement of the right kidney. An area of calcification was present in the periphery of the right adrenal. The epiphyseal age was determined as being between 15 and 16 years. The androgens in the urine were increased.

Shortly after the initial examination, his condition became slightly worse, and because an Addisonian crisis was suspected, large amounts of aqueous adrenal cortex extract (Eschatin), normal saline solution, and 5 per cent glucose solution were administered intravenously. This therapy had to be continued for several days, during which time myocardial fibrillation occurred several times. This was controlled with digitalis.

When his condition had improved he was operated upon. At surgery, a large tumor was found which displaced the kidney downward and which was compressing the renal pedicle. The mass was the size of a newborn infant's head. Postoperatively, aqueous adrenal cortex extract, desoxycorticosterone acetate, and intravenous normal saline solution

*This patient has previously been reported by Dr. William A. Reilly,[15] who supervised his treatment.

were necessary in order to combat shock. The pathologic diagnosis of the tumor was "degenerated adrenal adenoma." Because of extensive degeneration it was not possible to be certain as to the malignancy of the tumor.

Subsequent Course.—In the months following surgery, the patient felt well, had an excellent appetite, good strength, and no loss of hair. There were no further nocturnal emissions or erections. The mother stated that the acne had improved, but there was no change in the size of the genitalia, nor in the depth of the voice. Six months after operation, the total ketosteroids were still elevated to 5.6 mg. per twenty-four-hour urine specimen, while at the age of 9 years, 9 months, they had risen to 10 mg. per twenty-four hours. The bone age was then at the same stage of advancement as had been present at the time of surgery; namely, between 15 and 16 years. Fig. 10*B* shows the patient in May, 1946. He was last seen in January, 1950. He was feeling fine and had no evidence of recurrence of his symptoms, although he was unhappy about his short stature.

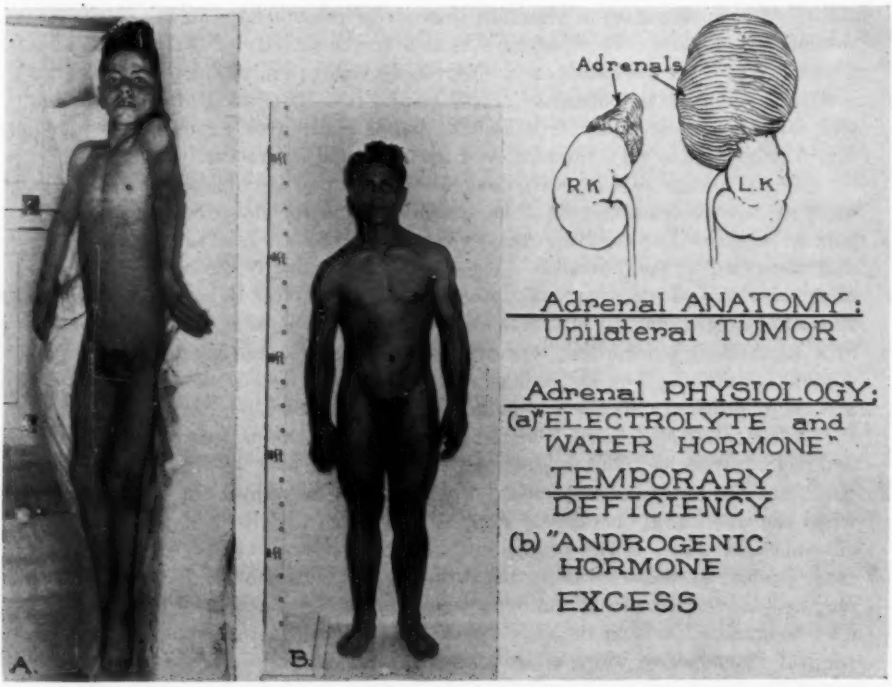

Fig. 10.—Patient (Case 7) with a unilateral adrenal adenoma. *A*, On admission to the hospital at the age of 6 years, 4 months. Patient was so weak that he had to be propped for photography. Note the adult-sized penis and copious hair. *B*, At 11½ years of age, five years after removal of the tumor.

DISCUSSION

These cases demonstrate the more pertinent clinical, laboratory, and pathologic findings of some of the syndromes associated with abnormalities in secretion of the adrenal cortex, and they indicate the aids to early diagnosis which

are available and the types of replacement therapy which can be used for successful treatment of cortical insufficiency.*

The symptoms of deficiency of the adrenocortical hormone may be the same regardless of whether they result from: (1) congenital hypoplasia (or acquired atrophy) of such a degree as to result in permanent inadequacy; (2) a temporary hypofunction of the cortex but with adrenals which subsequently function adequately; or (3) the congenital adrenogenital syndrome with hyperplasia of both glands with deficient secretion of those "cortins" which influence salt and water retention simultaneously with excess secretion of androgens which induce masculinization and precocious maturity.

In any case, the underlying pathologic physiology of a partial or complete hypofunction of the cortex is due largely to impaired intestinal absorption of water, sodium chloride, and perhaps of glucose, and an interference with the ability of various tissues to maintain the correct relationships in the concentration of various salts. There is also a change in the activity of the renal tubules which fail to conserve sodium and chloride by resorption, although favoring an abnormal retention of potassium. This results in a depression of blood sodium and chloride, an elevation of potassium, and is manifested clinically by vomiting, which often is very forceful, and by marked dehydration.

In each of our patients with congenital deficiency of cortical hormones, the most prominent symptoms have been vomiting and/or dehydration with poor gain of weight. The vomiting usually started within the first two weeks of life and was often of the "overflow" type at first. Gradually, however, it became more forceful and was frequently projectile in character. In some patients this type of regurgitation led to a diagnosis of pyloric stenosis and the performance of a Rammstedt pyloroplasty operation with, of course, no improvement in the clinical condition. The abdominal scar of the infant who continues to vomit after a pyloroplasty may be a "badge of adrenal insufficiency."

Adrenocortical deficiency should be suspected in the patient whose vomiting and dehydration is relieved during periods of repeated hospitalization when parenteral fluids are administered, only to have a resumption of the symptoms when the parenteral therapy is stopped. In these instances, it is the sodium chloride and water which produces the clinical improvement. This has been made evident by the knowledge that although complete control of the symptoms may require the use of natural or synthetic hormones, temporary or mild relief may be obtained both in the experimental animal and in the human being with cortical insufficiency when added amounts of salt alone are given either by mouth or parenterally. When the added salt is stopped, the symptoms recur.

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*From a review of adrenal disorders occurring in childhood, Wilkins[3] has drawn certain conclusions with which we would agree:

(1) Adrenal lesions occur four times as often in girls as in boys.

(2) Congenital androgenic hyperplasia is the most common disorder, accounting for two-thirds of all adrenal disturbances developing before the age of 10 years.

(3) In the case of lesions acquired *after* birth and before puberty, tumors are much more common than hyperplasia.

All of the cases reported in this age group in which there was virilization of previously normal females have proved to be due to tumor.

(4) Cushing's syndrome before the age of 10 years is not common, and when it does occur, it is almost always due to a tumor.

(5) In the cases of adrenal tumor developing before the age of 10 years, approximately the same number of patients had the adrenogenital syndrome as had Cushing's syndrome.

Poor appetite and resultant inadequate intake of food is another common symptoms in the Addisonian patient. However, the appetite for one substance, namely sodium chloride, may be increased. In one of our patients, the referring pediatrician suspected adrenal cortical deficiency and questioned the mother of the patient regarding an excess appetite for salt. The mother's reply was most enlightening since she stated that the child's sole interest in food was in salted crackers and potato chips. She had found quite by accident that he liked these foods and would lick the salt off them. Subsequently when salt was added to the child's milk, it resulted in immediate acceptance of two quarts a day whereas previously he had reluctantly accepted only one pint. This child, prior to salt therapy, also manifested the marked weakness so characteristic of Addison's disease in the adult.

The most alarming signs of adrenal insufficiency in children are those which result from vomiting, diarrhea, and anorexia with poor intake of food and loss of fluids. Dehydration is often very marked and if the replacement of fluids, salt, and deficient hormones is not started in time, death may supervene. In many instances, the degree of dehydration and signs of shock seemed out of proportion to the loss of fluids by vomiting or diarrhea.

Although pigmentation of the skin and mucous membranes has been mentioned prominently in published reports of adrenal insufficiency in adults, we have been impressed with the usual absence of this particular finding in the patients whom we have observed. Even in the infant who was found to have almost complete absence of the adrenal cortex at autopsy, there had been no definite increase in pigmentation at any time. The length of survival does not appear to be the governing factor in the degree of pigmentation of the skin since it has not become prominent in our patient who has been followed for more than six years for known cortical insufficiency. In one of our patients (W.K.), a female with pseudohermaphroditism and adrenal insufficiency, who is being adequately controlled by the subcutaneous implantation of desoxycorticosterone acetate pellets, excess pigmentation of the skin and gums has become evident. However, the mother of this child is an American Indian and the pigmentation may be partially on a racial basis rather than entirely the result of adrenal insufficiency.

Other signs and symptoms of insufficiency including hypotension, reduced body temperature, and diminished muscular activity have either been absent or so variable as to be of little value as aids in making an early definitive diagnosis.

Of particular interest in our patients with adrenal deficiency has been the frequent presence of marked eosinophilia of the peripheral blood. In some cases there appeared to be a direct relationship between the degree of insufficiency and the percentage and absolute number of eosinophiles, but in other instances the eosinophilia was independent of the clinical status of the patient at the time it was noted. Since our first observations regarding this relationship, Thorn, Forsham, and others have demonstrated the part that the adrenocorticotropic hormone of the pituitary (ACTH) plays in regulating the level of eosinophiles. They showed that when the adrenal cortex is present, the administration of ACTH causes a depression of eosinophiles (and less uniformly

of the lymphocytes). Thus it can be seen that when the cortex is absent or functioning inadequately, the controlling influence of ACTH cannot manifest itself in regulating the level of eosinophiles and so there may result an uninhibited rise of these blood elements.

The findings in our patients would suggest that this eosinophilia may be intimately regulated with that fraction of the adrenal having to do with salt and water metabolism. The child with the most striking elevation of eosinophiles (Case 1) had no increase in androgen excretion while other patients (Cases 2 and 3), who had excessive secretion of androgens at all times, demonstrated eosinophilia only when salt and water metabolism was disturbed. It is suggested that adrenal insufficiency be considered in a patient with unexplained eosinophilia, provided the rest of the clinical picture is consistent with this possibility.

A family history of pseudohermaphroditism, with or without accompanying evidences of adrenal insufficiency, may be an important aid in diagnosis. It was obtained in one of our cases and probably was present in another. Both were females with pseudohermaphroditism and adrenal insufficiency. In the first, an older sibling had had a similar abnormality of the genitalia and had died at the age of 4 months from adrenal insufficiency; while in the second case, the older sibling was a male who had begun to vomit at 3 weeks of age and had died after several weeks' illness—on the day he was scheduled for operation for a presumed pyloric stenosis. In both families there were other normal children. A familial occurrence of adrenal hyperplasia has been reported frequently in the literature of pseudohermaphroditism, and has always been limited to only one generation. Furthermore, in no instance did either parent present definite evidence of any endocrine disturbance.

The characteristic blood chemical findings in all of our patients with adrenal cortical insufficiency consisted of a depression of the sodium and chloride and an elevation of the potassium. The nonprotein nitrogen usually was elevated before therapy was instituted. However, the fasting blood sugar which is characteristically low in classical Addison's disease never was found to be depressed in our patients in whom deficiency of cortical hormone produced a disturbance of salt and water metabolism. This lack of hypoglycemia was noted even in the child who, at autopsy, was found to have almost complete absence of both adrenal cortices.

Excess androgen secretion by the adrenal cortex is manifested by acceleration in the appearance of the epiphyseal centers, accelerated growth in the length of the long bones, precocious sexual development, and abnormally high excretion of 17-ketosteroids in the urine. The increased growth may be apparent very early in life, and may be maintained at a fairly uniform rate (see Fig. 7), or there may be a lag before it becomes manifest, due presumably to the inhibiting effect of the poor general nutrition that is associated with the Addisonian deficiency. The case of J. M. illustrates this delay of advanced growth. In this patient, growth, as well as the time of appearances of the various epiphyseal centers, was normal during the first year. Subsequently, however, they began to be markedly accelerated so that by 5 years of age his bone age was advanced beyond 12 years, and at the age of 6 years this child was 6½ inches (16.5 cm.)

taller than the average boy at the same age and 4½ inches (11.4 cm.) taller than 90 per cent of boys his age.[13] From this it may be seen that although increased stature may result from androgenic excess very early, this is not necessarily true in all cases and so the diagnosis of androgenic excess cannot be ruled out merely because the patient has normal or even slower than normal growth during the first year of life. Likewise, the presence of normal maturation of the epiphyseal centers during the first months of life does not rule out the presence of increased androgen secretion by the adrenal cortex.

Enlargement of the genitalia also may not be marked for a period of several months. The malformation of the genitalia in female children is characteristic of the congenital form of the adrenogenital syndrome in which the excessive production of androgens by the adrenal acts in utero to produce development along masculine lines. In the females these changes are quite evident at birth, but in the males (cf. Case 3), who later showed a striking precocious maturation and changes of the genitalia, marked macrogenitosomia may not be present in the newborn period, even though it manifests itself soon thereafter. However, in all of our cases where excess androgen activity eventually was demonstrated clinically, the excretion of 17-ketosteroids in the urine was abnormally high, even in early infancy, and this abnormal excretion has been the only reliable clinical or laboratory finding which could be counted upon to indicate increased androgen activity in the first year of life.

Although these children will show accelerated rate of growth and will be much taller than the average for their age during the first few years of life, the acceleration in the maturation of their epiphyses progresses at a still more rapid rate. This disproportion between the rate of growth and the rate of epiphyseal maturation ultimately results in short adult stature following exceptional tallness as a child.

It is also interesting to note that in those children who had precocious epiphyseal development, the eruption of the teeth was not advanced: it occurred at the normal time and in the normal sequence. The 6-year-old boy with the bone age of 12 years (Case 7) did not have any permanent teeth erupting until after his sixth birthday.

The exact details regarding replacement therapy of these patients with insufficiency of cortical hormones are not presented here since such wide variations in the amounts of various therapeutic agents are needed for individual patients, that no standardized routine can be indicated. In general, it was found that the initial treatment was best carried out with the generous use of whole adrenal cortical extract, both aqueous and lipoid, given by injection along with the addition of sodium chloride and sodium bicarbonate to the diet. In almost all cases normal saline solution was given parenterally. After initial control had been established, desoxycorticosterone acetate was started by the sublingual route, and the administration of adrenal cortical extract could then be discontinued after a period varying from a few days to several weeks. When initial control was reached, desoxycorticosterone acetate with or without added sodium chloride orally was usually sufficient to carry the patient along. When the patient was doing well on a set dose of oral desoxycorticosterone, the sub-

cutaneous implantation of pellets of desoxycorticosterone acetate usually permitted the cessation of sublingual medication except when it was needed during periods of special stress.

In determining the maintenance dose of desoxycorticosterone acetate that was needed, it seemed advisable to keep it at such a level that supplemental sodium chloride would be necessary for complete control of symptoms. This appeared especially important in a child being controlled by implanted pellets alone. If added salt was necessary in the diet for complete maintenance, it would be possible to overcome the effects of hormone overdosage, such as edema, etc., by temporary withdrawal of the added salt. Were regulation accomplished without the need for supplemental sodium chloride, the effects of overdosage could be counteracted only by the surgical removal of the pellet. Although we attempted to maintain the dose of desoxycorticosterone at a level where additional sodium chloride in the diet would be necessary, in most of the cases this was not accomplished since surprisingly small dosages resulted in control of the condition.

From a study of patients with cortical insufficiency we have been impressed by the fact that they respond to replacement therapy in much the same way as the untreated child with diabetes responds to initial therapy with insulin. The dosage of medication that is necessary at the beginning of therapy usually is much greater than the amount which will eventually be necessary for maintenance. This has meant that in the patient suspected of having adrenal cortical insufficiency, it often is necessary to continue therapy for several days and to give very large amounts of cortical extract and of parenteral fluids before a noticeable effect is obtained.

In treating patients with adrenal insufficiency with the various preparations that may be used, the problem of overdosage is a very real one. Grollman has stated that "no good evidence has been adduced to demonstrate any effects from an overdosage of the (adrenal cortical) hormone in the normal animal other than a suppression of the animal's own adrenals. When administered in excess, the hormone is probably excreted in the urine." But even though treatment with excessive amounts of the whole hormone would thus appear to be entirely safe, the administration of certain synthetic and natural fractions of the hormone is not free of danger. Thus, the prolonged administration of excessive amounts of desoxycorticosterone may produce hypertension, pathologic changes in the brain, heart, and kidney, as well as abnormal retention of sodium and loss of potassium. Some of the findings in one of our patients who died, and on whom postmortem pathologic studies were made, were probably due to overdosage with the desoxycorticosterone acetate. Another disadvantage in the use of desoxycorticosterone is that it fails to remedy the defect in carbohydrate metabolism, and so, ideally, would not be used as the exclusive therapeutic agent in a patient with that abnormality. Clinically, it has been found that it may be used without other hormones in the treatment of chronic cortical insufficiency with satisfactory results, although in the initial stabilization of the patient or for an acute crisis, additional agents will usually be found desirable.

The remarks made do not take into consideration an entirely different type of adrenal extract than those referred to thus far; namely, cortisone or compound E. It is already apparent that the patient with Addison's disease is immensely helped by remarkably small doses of this substance, and that in the future it will play an important role in the treatment of Addisonian crisis, even though it may not be so suited to therapy beyond the acute stage.

It will interest those handling cases similar to those described to know of our experience using adrenocorticotropic hormone (ACTH) in three of these cases, as a diagnostic aid. Cases 2, 3, and 5 were studied at a time when each was under therapy and in good control. ACTH from both Dr. Li in Berkeley and the Armour Company was given intramuscularly in the amount of 1 mg. per 5 pounds. Initial blood eosinophile counts (in counting chambers 0.2 mm. deep) were compared with counts four hours after the injection. In each of the six instances, save one (in which there was a slight rise), a fall in eosinophiles occurred, but the decrease was between only 4 to 37 per cent. This was less than the decrease expected in normal individuals which Forsham and collaborators[16] have shown to be in the range of 52 to 98 per cent. In three control cases a normal response was obtained, the decrease being 64, 77, and 87 per cent, respectively.

The failure to obtain a normal reduction of blood eosinophiles following ACTH administration, therefore, confirmed the abnormality known to exist in adrenal glands of the three patients studied.

SUMMARY

This paper deals with the clinical, chemical, and pathologic findings of seven children who presented abnormalities in secretion of the adrenal cortex. All cases, save one, were congenital in origin.

Five of these patients presented the picture of insufficiency of the substances regulating salt and water metabolism. In each of them the most prominent symptoms were dehydration with poor gain of weight and/or vomiting. The latter often was projectile in character, and in the young infants sometimes led to an erroneous diagnosis of pyloric stenosis. Pigmentation of the skin and mucous membranes was not a prominent finding. The characteristic blood findings consisted of a depression of sodium and chloride and an elevation of potassium. The fasting blood sugar was normal. Four of the five patients with adrenal insufficiency have been successfully controlled with the help of supplemental replacement therapy for periods up to six and one-half years.

One patient with congenital Addison's disease died at the age of 10 months. Post-mortem study showed almost complete absence of the adrenal cortex and vascular changes of the kidneys, which probably resulted from overdosage with desoxycorticosterone acetate which had been given for the adrenal deficiency.

Marked eosinophilia of the peripheral blood was present in several patients with adrenal insufficiency, and it is suggested that this abnormality be considered in certain patients with unexplained eosinophilia. Whatever the blood eosinophilia level may be, the manner in which injection of adrenocorticotropic hormone affects it constitutes a useful test of adrenal function, as pointed out by Forsham and collaborators.[16]

In three patients excessive secretion of adrenal androgenic hormones was present simultaneously with the previously mentioned insufficiency of adrenal salt- and water-controlling hormones. Two of these patients were females in whom pseudohermaphroditism was thus produced. The other was a male with sexual precocity.

Increased androgen secretion by the adrenal cortex was manifested by acceleration in the appearance of the epiphyseal centers, accelerated growth in the length of the long bones, precocious sexual development, and abnormally high excretion of 17-ketosteroids in the urine. The eruption of the permanent teeth was not markedly advanced in the 7-year-old patient with other evidences of precocious sexual and physical maturation. The increased excretion of 17-ketosteroids may be the only abnormal finding which is evident during the first year of life in a male patient with the adrenogenital syndrome.

A family history of a similar condition was found in two of our female patients with pseudohermaphroditism and adrenal insufficiency. Knowledge of such previous familial occurrence may be of considerable help in the early recognition of congenital adrenal abnormality.

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INFANT AND MATERNAL MORTALITY IN SAN FRANCISCO

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TWO decades bring about many changes in the life of a community. San Francisco has shared, with the whole nation, the dramatic changes of the past twenty years. The community has passed through and recovered from a long period of economic depression, embarked upon a whole-hearted participation in war activities, both in industry and in military service, and finally emerged upon a period of rehabilitation, which, five years after the end of the war, is still making demands upon the citizenry and bringing new changes. Less spectacular and far less publicized has been the steady flow of life through the community. Thousands of babies have been born. Many of them have died in the first year of life, and unfortunately the life of the mother also has been sacrificed in some instances. It is to these vital events in the city's growth that attention is called in this study.

Five different years, at five-year intervals, have been selected out of the last twenty as a basis for the statistical data presented:

1930—a normal year, before the economic decline gained momentum;
1935—a year at the very depth of the depression;
1940—a year unaffected by war-motivated influences that were to follow;
1945—a year that saw the end of the war and the beginning of a period of rehabilitation;
1949—a year of latest available statistics, five years beyond the war period.

For the first five years of this twenty-year period the trend in birth rates was definitely downward, reaching its lowest level in 1935. Then began a gradual rise, accelerated by an influx of war industry and service personnel. By 1947, the birth rate reached an all-time high of 22.6 per 1,000 population, and has continued at approximately this high level to the present time (Fig. 1).

The natural inference is that many families brought into the community by war activities have remained. A racial breakdown of the figures indicates that in the last five years the increases have been entirely in the Negro, Chinese, and other nonwhite groups. Birth rates for the white portion of the population have declined steadily since 1940 (Table V). Further emphasis of this growth in the nonwhite segment of the population is found in the racial breakdown on infant mortality (Table IV).

This may have been a factor leading to an optimistic estimate of population for San Francisco, but there can be no quarrel with the fact that the last five years have brought about significant changes in the composition of the

Director, City and County of San Francisco Department of Public Health.

population and the increment is found in the Negro and Chinese groups. Slight increases are similarly noted in the Japanese group following the return of the evacuated Japanese at the close of the war. It will be of interest to learn whether or not the forthcoming federal count will support these statements.

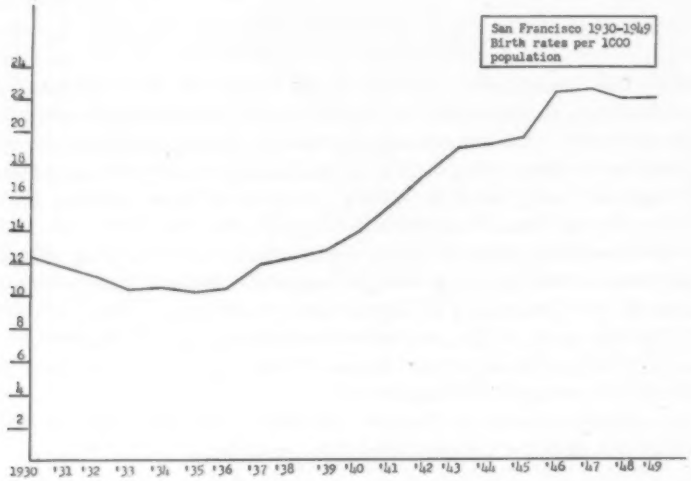

Fig. 1.

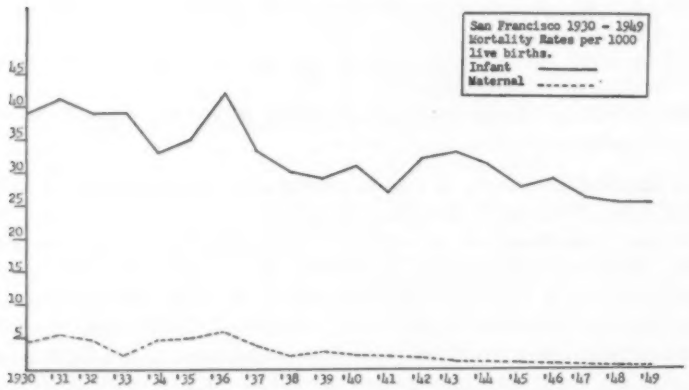

Fig. 2.

The infant mortality rate for San Francisco (Fig. 2) has for many years been as low, if not lower, than the corresponding rate in other large metropolitan areas. At no time during the past twenty years has this rate reached either the state or national level. The infant mortality rate for 1949 shows a 36 per cent decrease from that of 1930—and the decline has been fairly consistent (Table I). The rise in 1936, the peak year of the period, may be traced to an

outbreak of infant diarrhea, which resulted in 20 deaths, or 7 per cent of the total infant deaths for that year. Eleven of these deaths occurred in the neonatal group. About three-fourths of all infant deaths each year occur in the first month of life (Table II).

TABLE I

YEAR	BIRTHS (TOTAL)	INFANT DEATHS		MATERNAL DEATHS	
		TOTAL	RATE*	TOTAL	RATE*
1930	7,903	315	39	35	4.4
1931	7,646	318	41	39	5.1
1932	7,410	293	39	34	4.5
1933	7,002	275	39	20	2.8
1934	7,159	238	33	32	4.5
1935	7,123	252	35	33	4.6
1936	7,285	304	42	18	5.7
1937	8,223	268	33	31	3.8
1938	8,509	252	30	19	2.2
1939	8,817	256	29	25	2.8
1940	8,814	274	31	19	2.2
1941	9,812	269	27	21	2.1
1942	12,587	396	32	26	2.1
1943	14,771	486	33	17	1.2
1944	14,904	459	31	18	1.2
1945	16,114	446	28	20	1.2
1946	18,558	531	29	19	1.0
1947	19,751	517	26	16	0.8
1948	19,253	473	25	15	0.8
1949	19,271	477	25	12	0.6

*Rates per 1,000 live births.

TABLE II. AGE DISTRIBUTION

AGES	1930			1935			1940		
	TOTAL	PER CENT IN GROUP	CUMULATIVE PER CENT	TOTAL	PER CENT IN GROUP	CUMULATIVE PER CENT	TOTAL	PER CENT IN GROUP	CUMULATIVE PER CENT
Under 1 day	106	33.7		101	40.1		111	40.5	
1 to 6 days	62	19.7	53.4	60	23.8	63.9	53	19.3	59.8
7 to 30 days	42	13.3	66.7	29	11.5	75.4	45	16.4	76.2
1 to 11 months	105	33.3	100.0	62	24.6	100.0	65	23.7	99.9
Total	315			252			274		

AGES	1945			1949		
	TOTAL	PER CENT IN GROUP	CUMULATIVE PER CENT	TOTAL	PER CENT IN GROUP	CUMULATIVE PER CENT
Under 1 day	168	37.7		181	37.9	
1 to 6 days	130	29.1	66.8	123	25.8	63.7
7 to 30 days	53	11.9	78.7	51	10.7	74.4
1 to 11 months	95	21.3	100.0	122	25.6	100.0
Total	446			477		

The greatest single cause of infant deaths is prematurity (Table III). In 1945, there were 1,032 babies born prematurely with 191 deaths (18½ per cent) in which prematurity was given as the cause. In 1949, there were 216 deaths of premature infants, 14½ per cent of the 1,481 babies born prematurely. It is a very obvious fact that the longer the period of gestation the better the

TABLE III. CAUSES OF INFANT DEATH

CAUSE	1930		1935		1940		1945		1949	
	UNDER 1 MO.	UNDER 1 YR.	UNDER 1 MO.	UNDER 1 YR.	UNDER 1 MO.	UNDER 1 YR.	UNDER 1 MO.	UNDER 1 YR.	UNDER 1 MO.	UNDER 1 YR.
Prematurity	106	110	107	108	110	112	190	191	214	216
Atelectasis, etc.	25	28	28	32	24	28	59	60	46	49
Congenital malformation	29	46	25	35	35	51	45	72	44	89
Communicable disease	1	12		5		1	1	4		4
Congenital syphilis	3	3	3	4	-	-	2	2	-	-
Respiratory disease	10	47	1	23	3	17	12	37	7	19
Diarrhea-enteritis	2	10	2	5	7	8	2	5	2	8
Suffocation in bed	1	3	-	4	1	5	5	19	-	20
Other accidents		2	1	2	1	2	3	5	1	10
All other causes	33	54	23	34	28	50	32	51	42	62
Total	210	315	190	252	209	274	351	446	355	477

chances of life. For this reason, if for no other, efforts should be directed to eliminate all known causes which bring about prematurity. Good prenatal care is of basic importance.

Another cause of infant deaths which shows a rather significant rise over the period is accidental suffocation in bed or cradle (Table III). This might properly fall into the category of preventable home accidents, and the exercise of greater precaution in the home would, without question, reduce the present high fatality rate in this classification.

TABLE IV. RACIAL DISTRIBUTION

COLOR	1930			1935			1940		
	UNDER 1 MO.	UNDER 1 YR.	PER CENT IN GROUP	UNDER 1 MO.	UNDER 1 YR.	PER CENT IN GROUP	UNDER 1 MO.	UNDER 1 YR.	PER CENT IN GROUP
White	201	293	93.0	181	237	94.1	195	257	93.8
Negro	-	1	0.3	2	3	1.2	3	3	1.1
Chinese	5	16	5.1	6	11	4.4	6	9	3.3
Japanese	4	5	1.6	-	-		3	3	1.1
Other	-	-		1	1	0.3	2	2	0.7

	1945			1949		
	UNDER 1 MO.	UNDER 1 YR.	PER CENT IN GROUP	UNDER 1 MO.	UNDER 1 YR.	PER CENT IN GROUP
White	322	401	90.0	283	384	80.5
Negro	22	37	8.3	48	62	13.0
Chinese	5	6	1.3	15	23	4.8
Japanese	-	-	-	-	1	0.2
Other	2	2	0.4	6	7	1.5

TABLE V. BIRTHS BY COLOR AND PERCENTAGE OF TOTAL BIRTHS

YEAR	WHITE		NEGRO		CHINESE		JAPANESE		OTHER	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
1949	16,062	83.3	1,746	9.1	1,122	5.8	128	0.7	213	1.1
1948	16,310	84.7	1,631	8.5	996	5.2	121	0.6	195	1.0
1947	17,608	89.1	1,416	7.2	493	2.5	84	0.4	150	0.8
1946	16,935	91.3	1,059	5.7	372	2.0	60	0.3	132	0.7
1945	14,897	92.4	790	4.9	314	2.0	5	- -	108	0.7
1940	8,379	95.1	53	0.6	269	3.0	68	0.8	45	0.5
1935	6,728	94.5	45	0.6	225	3.2	74	1.0	51	0.7
1930	7,321	92.6	36	0.5	382	4.8	126	1.6	38	0.5

Although the annual births have been steadily rising throughout this period, a remarkable decrease is observed in the maternal death rates. In 1930, in every 250 births one mother died; in 1949, one maternal death occurred in every 1,700 births. Good obstetrics and proper hospitalization have been important factors in reducing maternal risks in childbirth. At the present time 99½ per cent of the mothers are hospitalized, whereas in 1930, only 84 per cent were hospital births. Abortions, placenta previa, puerperal sepsis, and eclampsia are principal causes of maternal mortality.

This is the rather enviable record of accomplishment in San Francisco over the past twenty years. Much has been done to obtain these results, and must still be done to maintain existing standards. Full credit should be given to all those who have assumed a responsibility in promoting maternal and child health. Outstanding among these are the hospitals—both public institutions and those privately controlled, the varied activities of the Department of Public Health, and the private physician.

With practically all births occurring in hospitals, it is mandatory that nurseries and maternity wards be maintained at a high level of efficiency. Local hospitals, in cooperation with public agencies, and private physicians have taken a full measure of responsibility in reducing the high infant and maternal fatality rates.

The Department of Health has developed many programs in connection with maternal and child welfare. Among them is the constant supervision and inspection of drinking water and milk to the end that a safe supply of both is available in the community. Child welfare centers have been established in various parts of the city. These afford prenatal and postnatal care for mothers and provide instruction and guidance in the care of the child. Well-developed programs in the control of communicable diseases is another service offered the mother and child.

Under the leadership of such an outstanding pediatrician as Dr. Langley Porter, the private physicians in San Francisco deserve much of the credit for setting and maintaining the high standards which are the basis for the record made. The development of excellent feeding procedures for the baby, good prenatal care of the mothers, and regular follow-up on individual cases all are part of the routine of the private physician which has made these results possible.

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

ORVILLE F. GRIMES, M.D., H. GLENN BELL, M.D., AND MARY B. OLNEY, M.D.
SAN FRANCISCO, CALIF.

THE modern concept of the pathologic anatomy of congenital hypertrophic pyloric stenosis stems from the papers of Hirschsprung (1888).[1] However, at least two reports indicate that the condition was recognized in adults prior to that time (Landerer,[2] 1879, and Maier,[3] 1885). The earliest known reference to the disease was that by Beardsley whose accurate description of the condition appeared in 1788 in the earliest volume of medical transactions issued in this country entitled, "Cases and Observations by the Medical Society of New Haven County in the State of Connecticut." Because of widespread interest in this disease, Beardsley's report was later republished.[4] Within the decade following Hirschsprung's report, some twenty case histories were collected from the world literature[5] and by 1902 a total of fifty cases had been recorded, in nineteen of which operation had been performed.[6]

Various operative procedures were described and practiced prior to the turn of the present century. Loreta[7] (1887) performed a divulsion of the pylorus and introduced graduated sounds through an incision in the gastric wall in an attempt to dilate the pyloric canal. Rather than dilating, the stenotic area usually ruptured and produced a uniformly fatal peritonitis. Simple pyloroplasty (Cautley and Dent,[8] 1902), consisting of conversion of a longitudinal incision into a transverse one in the manner of the Heineke-Mikulicz procedure, was popular for only a short period. The incision extended through the entire pyloric tumor into the stomach and duodenum, and peritonitis again was the most common cause of failure. Gastroenterostomy was a logical procedure in the early surgical treatment of hypertrophic pyloric stenosis because it was a popular choice for treating allied conditions in the adult. Even though diligent efforts resulted in a steadily decreasing mortality rate, it still remained higher than the reasonable rate for abdominal procedures. Research therefore was directed toward the exploration of the various types of pyloroplasties, culminating in the submucous pyloroplasty (Fredet-Rammstedt procedure) which has few peers with respect to its merit and practical results in the annals of surgical practice.

The value of extramucous pyloroplasty in the treatment of congenital hypertrophic pyloric stenosis cannot be denied. Pierre Fredet[8] must receive credit for the basic essential of the operation: the longitudinal incision of the serous and muscular layers of the pylorus without injury to the mucosa. The operation he described in 1908 included the conversion of the longitudinal incision into a transverse one by suturing. Conrad Rammstedt,[9] in 1912, first omitted closure of the incision, allowing the pyloric wound to gape widely without further manipulation. Although this modification is the operation in universal use in modern surgery, both pioneers should receive their due. The Fredet-Rammstedt operation for hypertrophic pyloric stenosis is their monument.

From the Divisions of Surgery and Pediatrics, University of California School of Medicine.

It has been shown that the size of the pyloric tumor is due entirely to the greater bulk of muscle tissue in the circular layer; the connective tissue separating the muscle cells is not increased. The absence of inflammatory reaction in the mucosa suggests that the obstruction from the tightly closed pylorus is responsible for the predominant symptom of vomiting. The rationale of the operative procedure is based on the fact that the thickening of the pylorus is due to an increase in the muscular coat, the other layers remaining entirely normal. Because smooth muscle cells regenerate minimally, if at all, the space between the margins of the Fredet-Rammstedt pyloric incision is filled by the connective tissue which arises in the serosa and submucosa (Fig. 1).

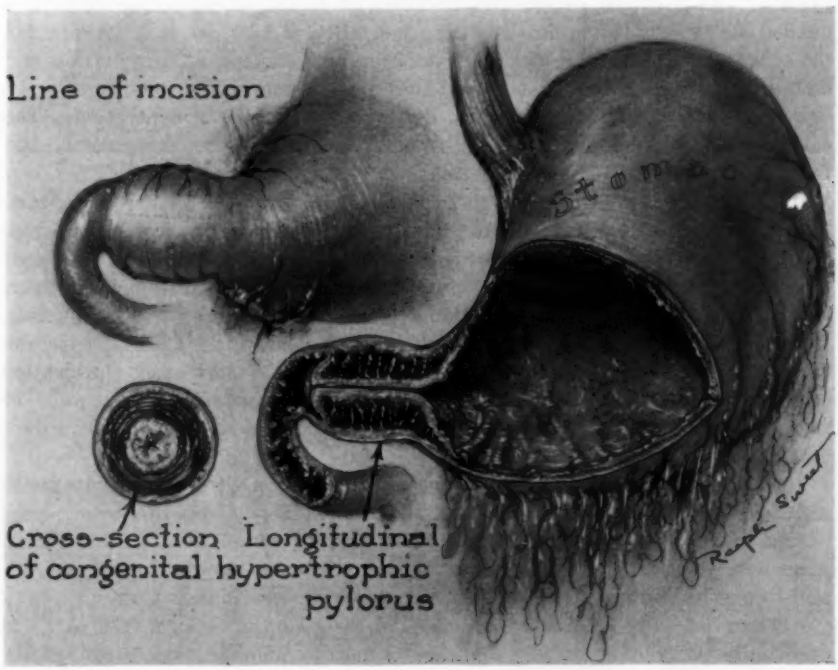

Fig. 1.—An avascular area can be identified on the pyloric tumor through which the incision is made. The hypertrophied musculature is sharply demarcated in its duodenal portion, but gradually blends into the gastric wall proximally. The dilatation of the stomach is evident.

The symptomatology of the disease presents a most striking uniformity. The well-known features of projectile vomiting, marked constipation, visible upper abdominal left to right peristaltic waves, loss of weight in spite of feedings which are most eagerly taken, are observed in an infant well nourished at birth. Vomiting characteristically is delayed beyond the first or second week of life inasmuch as the growth of the pyloric tumor, which produces the obstruction, is apparently progressive. The pyloric tumor is frequently but not necessarily palpable. The infant's course is steadily downhill once symptoms become evident.

Operation is followed by gradual relaxation of the muscular layer from the relief of the obstruction and the cessation of the constant stimulation of its contractile power. The connective tissue proliferating in the gap between the incised margins contracts so that the divided ends of the muscle coats tend to approach each other and the space between them gradually decreases. As early as twenty-five days after surgery, there is but a narrow scar indicating the site of the pyloric incision, and after eighteen to twenty-four months, the scar becomes practically invisible.[10]

One of the earliest publications reporting the results of the surgical treatment of pyloric stenosis by the Fredet-Rammstedt procedure is that of Downes[11] (1920).* In a review of the case histories of infants operated upon by this method, he reports thirty deaths with a mortality of 17.1 per cent. A clue for the subsequent recognition and understanding of the effects of dehydration and malnutrition is given by the statement that in infants operated upon four weeks or less from the onset of symptoms, the mortality was only 8 per cent. The causes of death included acute gastroenteritis, peritonitis, hemorrhage, and for a lack of a better term, marasmus.

It is of interest to contrast these results with those of more recent years. The basic surgical technique has not been altered by the passage of time. From July, 1930, to July, 1950, at the University of California Hospital, 113 patients have been operated upon for congenital hypertrophic pyloric stenosis without a single fatality. Comparable results have been reported elsewhere in America. Credit for this outstanding achievement is due not only to the standardization and perfection of the operative technique, but also to a more exact clarification of the effects of starvation and dehydration. The painstaking preparation of these patients for surgery has become the most important single problem in their care.

Of the 119 infants admitted to the University of California Hospital with a definite or presumptive diagnosis of pyloric stenosis during this twenty-year period, six were not operated upon. Four received conservative medical treatment with good results, one baby was signed out of the hospital by the parents, and in one having severe mongolism, the condition was found at autopsy.

There were 92 males and 27 females in the group, a ratio of 3.35 to 1. It frequently is stated that the condition is most common in first-born infants. This is true in this series. However, the number of second- and third-born infants is significant, suggesting that such a statement is only of relative value in the over-all evaluation of the problem. (Chart 1.) A positive family history of hypertrophic pyloric stenosis was obtained in 14 cases. (Chart 2.)

The number of infants demonstrating associated defects is of interest. The disease is commonly called congenital hypertrophic pyloric stenosis, even though the term "congenital" is a controversial one. Congenital defects must of necessity originate during the first three months of intrauterine life during the formative period of the organ systems. Pyloric stenosis, however, does not

*Dr. Langley Porter, to whom this edition of THE JOURNAL is dedicated, witnessed the first operation for pyloric stenosis performed by Downes in the United States. So far, as can be determined, the second such operation was on a patient of Dr. Porter's[12] in San Francisco, the operation being performed by Dr. Alanson Weeks.

occur until after the pregnancy is completed. If the disease were actually of congenital nature, the incidence of associated defects should be relatively high. In the entire group of 119 patients there were only 9 associated defects (Chart 3).

The greatest number of infants were between 3 and 8 weeks of age when admitted to the hospital for care (Chart 4). This agrees with the statistics recorded in most published papers, serving merely to emphasize that the disease is not commonly present during the first week of life, but becomes increasingly evident thereafter. It is encouraging to note that in the later years of the survey (1940 to 1950), a suggestive or positive diagnosis of pyloric stenosis shortly after the onset of symptoms resulted in there being a greater number of infants admitted to the hospital during the first three weeks of life.

The fact that in the majority of the infants, the duration of symptoms varied only from one to four weeks indicates that the problem of pyloric

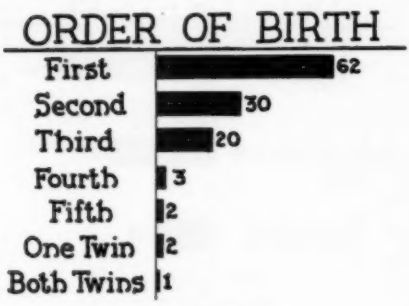

Chart 1.

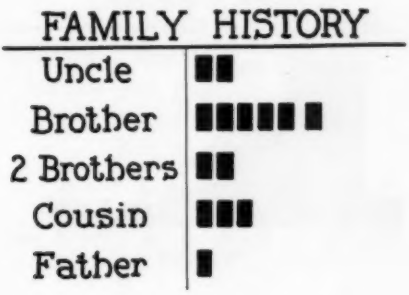

Chart 2.

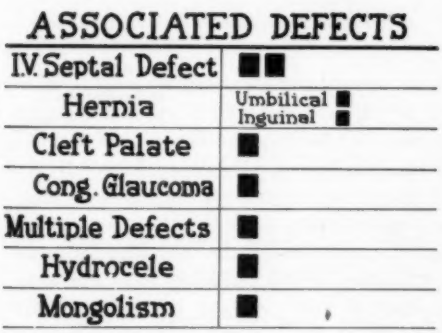

Chart 3.

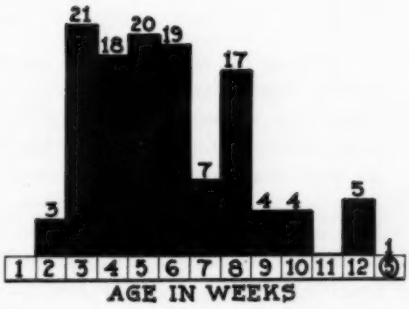

Chart 4.

Chart 1.—Note that in two sets of fraternal twins, pyloric stenosis occurred in one twin and not the other. In the entire series, the condition was present in both twins only once. These were identical twin boys.

Chart 2.—The occurrence of pyloric stenosis in other members of the family is not impressive.

Chart 3.—The use of the term "congenital" in the description of the condition can properly be contested, inasmuch as the number of associated defects in any reported series is significantly small.

Chart 4.—One infant was 5 months old when admitted for treatment. Most of the infants whose hospitalization was delayed had been treated as feeding problems.

stenosis in infants has become separated from vomiting in the newborn infant attributable to "feeding and formula" problems. (Chart 5.) The recognition and treatment of the effects of dehydration are evident in that only 20 of the 119 patients admitted to the hospital were considered to have a severe degree of dehydration. (Chart 6.)

The résumé of the case histories of these infants shows that the typical left to right upper abdominal, vigorous peristaltic waves were observed in all. However, a palpable tumor was discovered in only 81 of the infants, was questionably present in 26, and was not demonstrable in 12. (Chart 7.) It is not surprising that the pyloric tumor which is not only almost invariably subadjacent to the liver, but also lies deep within the abdominal cavity, is frequently difficult to palpate.

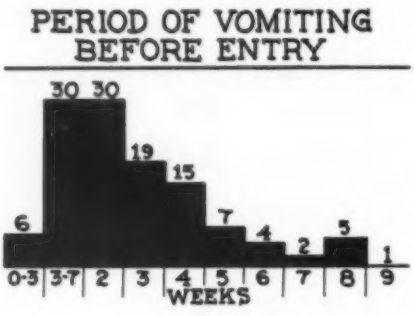

Chart 5.

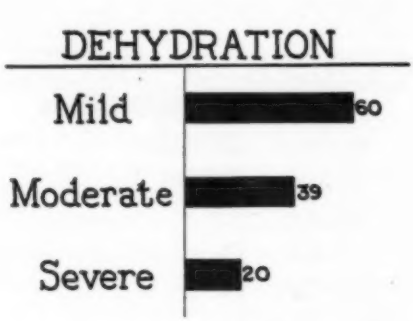

Chart 6.

Chart 5.—It is significant that the preponderance of admissions for vomiting have been made at an early period in the course of the condition.

Chart 6.—The recognition of the effects of dehydration and its treatment by adequate use of parenteral glucose and Ringer's solution have been of the greatest aid in the care of infants with hypertrophic pyloric stenosis.

During the early years of the period, several attempts were made to control the disease medically. In only 4 of 13 patients so treated was the therapy successful. Conservative therapy for a presumed feeding problem was instituted in 27 infants before the final diagnosis was established. However, especially in the later years of the period covered by the survey, a prompt diagnosis in most cases led to immediate preparation for surgery with no attempt at any other type of management. (Chart 8.) The fact that 96 of the 113 infants were operated upon within five days of their hospital entry indicates that not only was the diagnosis of pyloric stenosis established early, but also the necessity for early definitive surgery was recognized. (Chart 9.)

It was considered necessary in 27 instances to resort to roentgen studies in order to establish a diagnosis of pyloric stenosis. In each instance the stomach was carefully emptied by extensive lavage before surgery in order to prevent possible regurgitation and aspiration of the irritating barium mixture.

The operative procedure was similar in all of the patients. The greatest majority had the standard type of pylorotomy without division of the mucosa.

In order to study the histology of the thickened pyloric musculature, a small elliptical segment of the pyloric tumor was removed in a few cases. The clinical impression in the infants from whom the segment was removed was that of less regurgitation following surgery. A secondary operation was necessary in one infant who had been operated upon elsewhere with only partial division of the thickened pyloric musculature. At reoperation, the previously made pyloric incision was ignored. The usual Fredet-Rammstedt operation was performed through another area with excellent results.

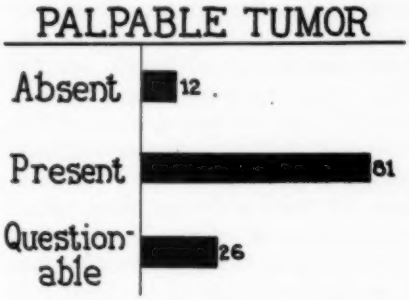

Chart 7.

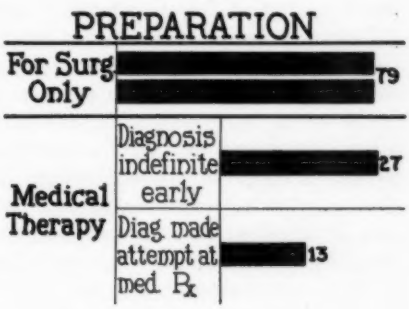

Chart 8.

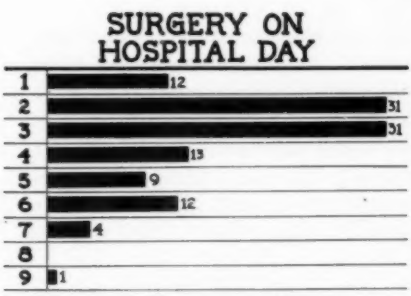

Chart 9.

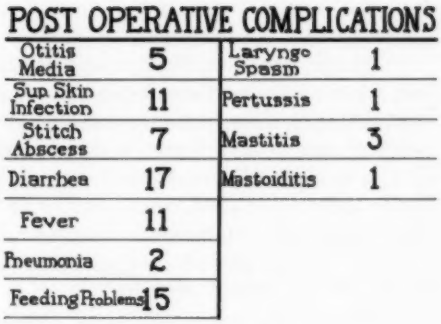

Chart 10.

Chart 7.—The high incidence of palpable tumors is attributable not to tissue wasting and relaxation but to patience in palpating after the infant has vomited.

Chart 8.—With early diagnosis and the recognition that the treatment is necessarily surgical, patients are now prepared for surgery directly without trial of conservative medical management.

Chart 9.—Indication of the recognition of the need for early definitive surgery.

Chart 10.—None of the postoperative complications failed to respond rapidly and adequately to proper therapy. In a significant number of infants, several types of formula were administered in an effort to re-establish normal feeding routines.

Of the 113 operations, 105 were performed under general anesthesia; only 8 patients required local anesthesia because of their poor condition.

If the pyloric musculature is adequately divided, the period of postoperative regurgitation or "spitting up" is short. The division of the hypertrophied musculature provides sufficient relaxation to permit the passage of

gastric contents. That relaxation is not immediately complete is evidenced by the fact that minimal regurgitation occurred in 105 of the infants following pylorotomy. The associated spasm subsides gradually to allow normal functioning of the pyloric sphincter. Moderate postoperative regurgitation occurred in only 2 infants, moderately severe in 5, and only 1 infant had persistent regurgitation (one month after surgery).

Postoperative complications occurred in a significant number of cases (Chart 10), although most of them were not of a serious nature. The incidence of minor complications was not greater than might be expected in any comparable series of major abdominal operations in other age groups. In no case did evisceration or severe wound infection occur.

Because the pyloric obstruction prevents the passage of liquids into the small intestine, starvation acidosis and dehydration constitute very important problems in the preoperative period. The subcutaneous administration of 3 to 5 per cent glucose in Ringer's solution, in amounts of 20 c.c. per pound of body weight, is adequate to combat simple dehydration and moderate loss of carbohydrates and chlorides from vomiting. If there is actual depletion of blood volume with impaired circulation, decreased kidney function, and deficient blood protein, then the circulating fluid may be bolstered with the intravenous administration of 10 per cent glucose, irradiated plasma, or typed whole blood in the amount of 15 c.c. per pound. The subcutaneous administration of 3 to 5 per cent glucose or normal saline also is necessary. Both procedures may need to be repeated several times at six- to eight-hour intervals to render the infant's condition safe for surgery.

Plasma or whole blood transfusions only rarely are necessary, but their use, when the indications are present, is imperative. It is important to remember that although these infants may be poorly nourished, their condition is not a surgical emergency. The time necessary to correct the effects of dehydration and to re-establish proper electrolyte balance is not only well spent, but absolutely essential if good results are to be obtained. Adequate preoperative care along with early diagnosis has served to diminish the morbidity and mortality rates of infants treated surgically for congenital hypertrophic pyloric stenosis to an almost insignificant level.

The use of general anesthesia, preferably open drop ether, is advantageous. The freedom from struggling allows one to perform a deliberate and careful operation, and the length of time the infant requires anesthesia is not great. Measures to combat the loss of body heat are essential and consist usually of the application of light wollen blankets about the extremities and the placing of a hot-water bottle beneath a large, flat, padded pan turned upside down, upon which the infant is placed for operation. Fluids are not routinely administered on the operating table since adequate hydration of the infant is assured preoperatively.

The operative procedure is well established in principle and performance. The danger point is, of course, at the duodenal end of the pyloric tumor. Here there is an abrupt end to the tumor and also the duodenal wall is much thinner than its gastric counterpart. We feel also that the use of the right rectus

incision is advantageous. By its use dehiscence and postoperative hernia formation are reduced to a minimum because the liver acts as a buttress against the suture line.

Because of the residual spasm of the pylorus in spite of the division of its hypertrophied musculature, and because of dilatation of the stomach in prolonged vomiting, the gastric emptying time for the first twelve to thirty-six hours may be delayed. For this reason, feedings are given in only very small amounts and at frequent intervals during this period, and increased cautiously as conditions permit. A 4 c.c. feeding eight to twelve hours postoperatively with 4 c.c. increments every two hours is practical. The choice of feeding is a readily digested formula, preferably low in fat so that the emptying time of the stomach will not be delayed. A three-hour regimen is instituted as soon after the operation as the tolerated volume of feeding permits. If distress or vomiting is encountered at any stage of the program, the next increment is not made. Elixir of phenobarbital in 2 c.c. amounts is administered at alternate feedings with the intent of sedating a hungry infant who is not yet able to tolerate sufficient calories to appease his appetite. The infants are fed with an eye-dropper until 30 c.c. feedings are given; they swallow very little air by this technique. When bottle feedings are initiated, the baby must be carefully burped to relieve him of the air he swallows. By the time of his discharge from the hospital on approximately the seventh postoperative day, the infant is able to tolerate the volume of formula of the four-hour feeding routine.

CONCLUSION

The Fredet-Rammstedt operation for congenital hypertrophic pyloric stenosis has both complete simplicity and absolute efficiency. The successful surgical treatment, however, depends largely upon adequate preoperative preparation designed to combat the effects of dehydration and starvation.

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TWO DIAGRAMS ON THE CLINICAL ENTITY

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THE accompanying pictorial diagrams have been designed to illustrate the concept of what physicians usually call the Clinical Entity. As all conceptual illustrations do, so do these diagrams emphasize certain aspects of their subject and neglect others. They may, therefore, be considered misleading. On the other hand, if a complex situation is, in general, only dimly illuminated, as is the case with the concept of the Clinical Entity, such diagrams help to shed light on essential features of that situation and to facilitate the right action. The diagrams given here have been found helpful in discussing with students that concept of their profession without which no clinician, be he a general practitioner or a specialist, a pediatrician or geriatrician, can "live, speak or act."[2]

The topic is treated in detail elsewhere.[3] In order to introduce the diagrams, the subject may be summarized as follows: The medical student, or for that matter anyone today who is interested in finding out what concept signifies the basic denominator in medicine (i.e., of course, clinical medicine) or how this basic denominator is constituted, faces the peculiar situation that hardly any modern information on these subjects is available. Medical textbooks deal solely with special topics. They are comparable to a textbook of physics or chemistry that would deal merely with descriptions of different atoms without discussing the present concept of the atom per se, or to a textbook of histology that would deal merely with descriptions of different cells without a presentation of the concept of the living cell per se. This lack of reference is not incidental. It is rooted in recent historical developments of medicine. It is due to the impact of the so-called exact natural sciences which have initiated an unparalleled progress in so many fields of medicine and from so many viewpoints and which have their basis in the inanimate world and the concept of the atom. Nevertheless, medicine cannot give up, and never has given up, the concepts of its immediate experience, such as life, development, ages, health, pain, disease, etc., concepts that have no place in physics and chemistry, yet will remain with medicine, whatever the physical-chemical correlates to these concepts may turn out to be. It is true, that during the course of medical history, physicians have developed numerous theories concerning the nature of these concepts and in particular the nature of disease. However, medicine is primarily and ultimately a practical endeavor of man and an exceedingly momentous one at that. Physicians are called upon to make fateful decisions on their individual fellow human beings. It is therefore not surprising to note that as medical historians report,[4, 6] dissenters in theory have often agreed on the practical approach to individual patients. It is the concept of the Clinical Entity which bridges the gap between the different theories of disease and thus is the basic standard of reference for all clinicians. It is the concept which attempts to comprehend a group of patients as similar and to serve in the single patient as an introductory step for

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arriving at an individual diagnosis. Research clinicians are concerned with the establishment of an actual Clinical Entity (which is not exclusively a statistical problem). They use single individuals as their material. Practicing physicians are concerned with the application of such an entity. They employ clinical entities as material to visualize the individual patient.

The concept of the Clinical Entity may be considered more or less identical with the concept of the Single Disease and on many occasions the terms Clinical Entity and Single Disease may be used interchangeably. In general, however, the concept of the Clinical Entity is both more inclusive and more precise from the clinician's point of view. It refers not only to a differentiation among sick people as the concept of the Single Disease exclusively does, but also to a differentiation among healthy ones, denoting so-called constitutional differences. Furthermore, the concept of the Single Disease does not necessarily express that uniformity of pathologic manifestations a physician needs as basis for his action; for instance, exudative and productive forms of tuberculosis of the lungs are differentiated as two clinical entities but may be considered to be one disease. The term entity is not fortunate. It has been meant to connote an existence independent from living structures.[1] Today the term is to be interpreted exclusively as meaning uniformity. As such it is well entrenched in the medical vocabulary.

After these introductory remarks, a structural analysis[7] of the concept—to borrow a phrase from the psychologists—will be more readily understood. Such analysis reveals that the Clinical Entity is a constellation made up of five factors. Using title heads of textbook sections as specific examples, one can characterize these factors as follows: I. The environmental factor (infectious diseases), II. the zoologic-constitutional factor, III. the topographic factor (disease of the cardiovascular system), IV. the morphologic, pathologic-morphologic factor (myocarditis, neoplasm of the heart), V. the physiologic, pathologic-physiologic factor (diseases of metabolism). Factors I and III to V do not require any further discussion on this occasion. It is the second factor whose significance is not clearly recognized today, and yet it plays a most important part in the physician's thought processes. For it revolves around the human organism as a whole, the initial and ultimate subject of all his efforts, and its core is those characteristics of that organism which, aside from questions of metaphysical attitude, are the most outstanding ones for the doctor—namely, the aging and dying of each human being, the irreversibly finite course of individual life. Individual life is not a whole at any of its moments, but is exclusively a whole for the entire period of its existence, from birth (conception) to death. It is a "Zeitgestalt."[8] "Nemo ante mortem beatus nominari potest," says the Latin proverb, "Nobody can be called happy before his death." This does not mean, of course, that life is a ghoulish dance toward death; it merely means that dying is implied in living, as the end is implied in a play or musical composition. In other words, death is not necessarily pathologic. As Paracelsus[5] expresses it, "There is no medicine for death, only for diseases." Thus historic

(rheic)* aspects of biologic dynamics must be differentiated from the aspects of dynamics of function per se, for the latter do not imply the aspect of course. They do not emphasize that individual life to a physician, to use a metaphor, is like a plane in flight, and the doctor like a plane mechanic who has to find out what is wrong with the plane during the flight. He is not like a car mechanic, who can, at will, stop the car at the curb and evaluate the fault after the stop. It is not the clinician, it is the pathologist who makes the examination after the journey is ended. The same aspects of historic (rheic) dynamics which apply to life in general apply to sick life with the following differences: Individual life always takes an irreversibly finite course, but what we call the pathologic processes in this same living organism may be reversible or irreversible, regressive, stationary or progressive. Disease, it may be said, is a play within a play and both patient and doctor are most interested in the type of ending of this secondary drama. The end of the original is known to everyone. It is the course of the second which poses the question. Will it lead to untimely pathologic death, will there be no end, i.e., the disease becomes chronic, or will it resolve itself? Prognosis ultimately is the most important part of diagnosis; as a matter of fact, closeness to death would be the keystone of any "natural system" of classification of diseases. To mistake one irreversible disease for another is not the basic error of the physician; the fundamental clinical error is to mistake a therapeutically reversible disease for an irreversible one and therefore to misdirect action. It may be reiterated again that this aspect of biologic dynamics is different from the functional one per se. Identical functional disturbances are not identical diseases as every physician knows. The uremia of an acute nephritis implies prognostic potentialities other than those of the uremia of a contracted kidney.

Thoughts like the ones presented are actually in the mind of each physician every day, although he may be only dimly conscious of them. The two diagrams are meant to illustrate these thoughts.

Diagram I represents a single organism or a group of organisms as a ball. The ball is shown in a cross section. The five factors of the Clinical Entity are marked as follows: *E* stands for the environmental factor and is represented by the whole area surrounding the ball; *C* stands for the zoologic-constitutional factor and is represented by the undulating line and the size of the ball; the latter is not particularly marked; *T* stands for the topographic factor and is represented by the layer of symbolic cells outlining the ball. In order to point out the different kinds of structures of which an organism is composed the cells have been shaped in different forms. *P.M.* designates the pathologic-morphologic factor. The different types of shading represent different types of pathologic-morphologic changes; for instance, the two cells with the oblique lines may indicate inflammation, the cells with the crossed line, carcinoma. The area inside the structural layer represents the fifth factor, the physiologic, and the area adjacent to the pathologic-morphologic site, marked *P.Ph.*, the pathologic-physiologic area. Intensities of pathologic-morphologic changes can be expressed by degrees of shade and intensities of pathologic-physiologic disturbances by the

*From rheo—I flow.

extent of the pathologic-physiologic area up to the center of the ball. The psychologic aspects of the organism and the psychologic origin of disease are by no means forgotten by the author, but no particular structures and functions of the organism are examined in this paper and a discussion of psychologic aspects would be a discussion of a particular characteristic, outstanding as this characteristic may be. In the diagram it could be represented by a color, perhaps of different intensity in different parts and of a different glow at different ages.

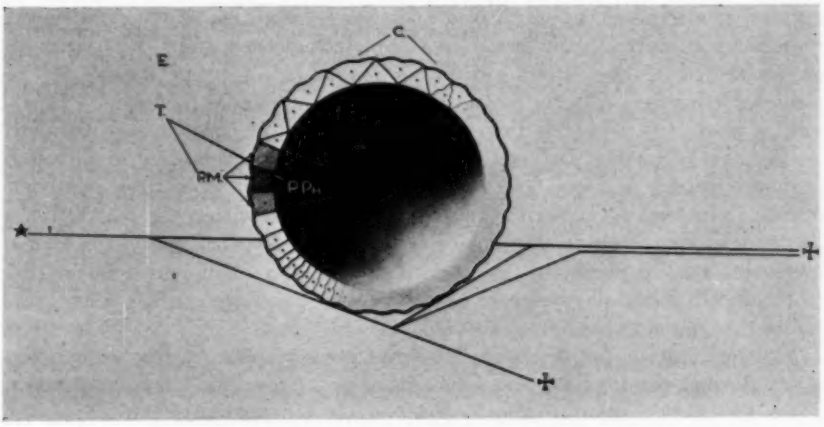

Diagram I.

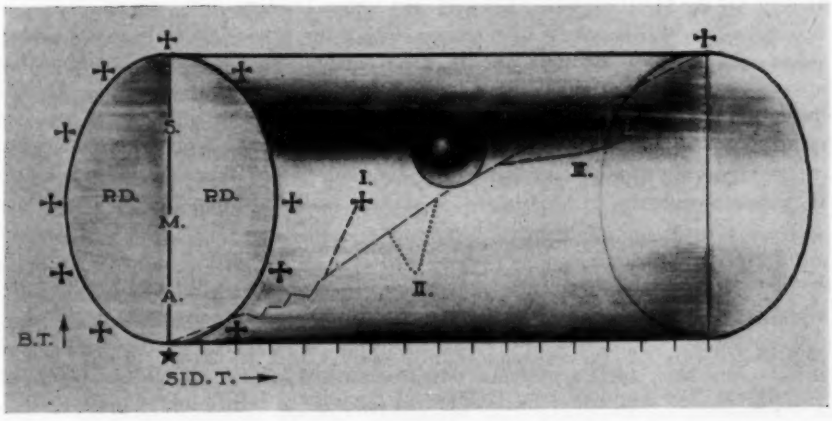

Diagram II.

The ball irreversibly runs from the left to the right, from the mark of birth to the mark of death. The play within the play, mentioned previously, may lead to untimely death as characterized by the lower mark of death, or the

disease may be entirely reversible, as manifested by the line leading back to the original line, or the disease may be reversible to a certain extent only and become stationary, as indicated by the line beneath the original line.

Diagram II emphasized particularly these aspects of flow. It shows a horizontal cylinder whose central plane is particularly marked. The x axis of this plane is subdivided to represent sidereal time. The y axis represents biological time; *A* stands for adolescence, *M* for maturity, *S* for senescence. The oblique line represents the course of life. The ball represents an organism or a group of organisms, as outlined in Diagram I. The area of the cylinder surrounding the central plane is the area of pathologic deviations, *P.D.*, with the circumference of the cylinder denoting pathologic untimely death. As the medieval hymn says, "In the midst of life we are surrounded by death" ("Media vita in morte sumus"). At the end of the life line, physiologic and pathologic death merge. Numeral *I* stands for the course of a disease leading to pathologic untimely death. Numeral *III* stands for the course of an entirely reversible disease. Numeral *II* marks the course of a deviation within the central plane, denoting a developmental disturbance, a type of disturbance that plays such an important role in psychiatry as, for instance, the so-called regression or drop to childhood levels of psychoneurotic patients. Psychoses, on the other hand, can be considered to be aberrations in depth.

A justification for discussing the presented problem hardly seems necessary. Several reasons have been enumerated in the previously presented paper.[3] From the viewpoint of medical education, and particularly with regard to medical students, a clear recognition of the concept of the Clinical Entity will point out those characteristics of the profession which make it genuine and not merely an appendix to physiology or any other branch of the science of man. It emphasizes those aspects of medicine which the physician and only the physician can properly evaluate and in the discrimination of which he alone will always be the master and the other workers in the field the servants. It will teach the student to arrange his thoughts in general, to understand what is meant by genuine observation in medicine and to prevent his mistaking mechanical enumeration of signs and symptoms for such observation. It will teach him to diagnose processes and not labels; in short, it will make him a better physician.

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OCULOGLANDULAR CONJUNCTIVITIS DUE TO LEPTOTHRIX

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IT IS the purpose of this paper to call attention to an ocular disease, possibly transmitted from cats, which produces a unilateral preauricular and submaxillary lymphadenopathy in children and young adults. This disease is a conjunctivitis due to leptothrix which is the most frequent cause of a syndrome of granulomatous conjunctivitis with associated regional lymphadenopathy, a syndrome generally referred to as Parinaud's oculoglandular conjunctivitis. Other granulomatous diseases may produce this syndrome, but leptothricosis, because of its predominant occurrence in the younger age group, is of especial interest to pediatricians. The general physical findings, with accompanying low-grade fever and an eosinophilia, together with therapy of this condition with sulfonamides, are discussed.

HISTORICAL SURVEY

In 1889, Parinaud[1] reported three cases of a form of unilateral conjunctivitis characterized by peculiar granulations with an associated regional lymphadenopathy and accompanied by fever. Occasionally, the affected glands would suppurate, but after a period ranging from a few weeks to several months the disease healed spontaneously, leaving no residual damage. Although Parinaud believed this disease was transmitted to the eye from animals, he had no bacteriological or pathological proof. The result was that all cases of conjunctivitis with granulation, ulceration, and regional lymphadenopathy were classed as Parinaud's disease, with no attempt to determine the etiology.

The distinctive histopathological features were pointed out by Verhoeff and Derby[2] in 1904, and the leptothrix was first recognized in sections of material taken from cases of Parinaud's conjunctivitis by Verhoeff.[3] In 1918,[4] he reported his observations on eighteen cases; in the same year Wherry and Ray[5] isolated the organism from material from the preauricular gland of a patient, an event which was repeated later by Wright.[6] The next important contribution was made by Verhoeff in 1940[7] when he described an improved method of staining the leptotriches of Parinaud's conjunctivitis. In 1944, Gifford and Day[8] reported twelve cases in which leptothricosis conjunctivae was suspected—all cases presenting the typical histological picture described by Verhoeff. Eight cases revealed leptothrix in sections with Verhoeff's modified Gram method. Material was cultured in three cases, and in only one of these was the leptothrix grown in culture, although in all three cases leptothrix elements appeared in sections of the conjunctival lesion. Therefore Verhoeff and Gifford and Day

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recommended biopsy examination as much more reliable in diagnosis than culture. Other literature contributions of note were made by Gifford,[9] Verhoeff,[10] Verhoeff and King,[11] Gifford and Dillon,[12] Theodore,[13] and Kant.[14]

CLINICAL PICTURE

Leptothricosis conjunctivae is a disease of the conjunctiva associated with enlarged preauricular and submaxillary lymph nodes and due to infection with the leptothrix. The disease is unilateral and occurs mainly in children with a history of exposure to cats. The source of infection is probably from cats, as this organism is frequently harbored in the tartar of the teeth of cats.

The constitutional symptoms are slight except for a low-grade fever and glandular enlargement associated with the onset of the ocular symptoms. A mild eosinophilia is a significant hematological finding.

The local subjective eye symptoms are mild and the conjunctival lesions appear as gray or yellowish necrotic areas beneath the epithelium. These necrotic areas are from ½ to 4 mm. in diameter and may be multiple or single, they may occur on any part of the conjunctiva and are sometimes associated with the formation of nodules and follicles. Ulceration of these lesions seldom occurs. The conjunctiva is edematous and congested, with secretion scanty or absent, and the cornea is not involved. The course is usually benign with spontaneous healing in one to three months, leaving no residual damage.

Several etiological agents may produce a clinical picture that resembles leptothricosis conjunctivae. They are:

1. Tuberculosis of the conjunctiva.
2. Oculoglandular tularemia.
3. Syphilis of the conjunctiva.
4. Lymphogranuloma venereum conjunctivitis
5. Sporothricosis.
6. Glanders.
7. Bacillus pseudotuberculosis-rodentium.
8. Soft chancre.
9. Vaccinia.

Each case of unilateral granulomatous conjunctivitis with lymphadenopathy should have several tests: (1) smears, scrapings, and cultures according to technique of Verhoeff and King; (2) guinea pig inoculation with ground up conjunctival material from site showing maximal pathology; (3) biopsy of conjunctival nodule; (4) Wassermann test; (5) agglutination test for tularemia; (6) tuberculin test, and (7) Frei test. Also a general physical examination for the presence of granulomatous disease elsewhere in the body should be done.

PATHOLOGY

Histologically, these lesions are subepithelial areas of necrosis in which the predominant cell is the macrophage in various stages of necrosis. These macrophages show fragmentation of the nuclei with a relatively small proportion of lymphocytes and plasma cells and almost no polymorphonuclear cells. Verhoeff has pointed out that the necrosis bears no relation to the caseation of tuberculosis

in that the macrophages are not confluent and the necrosis involves the cells alone. The surrounding area may show chronic inflammatory cells and varying amounts of granulation tissue. Irregular aggregations of very tiny unbranched filamentous microorganisms are present in the necrotic areas.

Verhoeff has shown that to demonstrate these organisms it is necessary to fix the tissue in Zenker's fluid. Sections from different levels should be stained slightly with hematoxylin and eosin, after which those sections showing the largest foci of macrophages should be stained by the modified Gram method. It is not necessary to decolorize these sections before thus restaining them.

Treatment in the past has been the excision of the gray areas and nodules. However, from my experience, it seems that sulfonamide therapy shortens the course of the disease considerably.

CASE REPORTS

CASE 1.—V. M. B., a 6-year-old white girl, consulted her pediatrician, Dr. George Sherman, because of enlargement of the right preauricular and submaxillary lymph glands. Although no ocular discomfort was mentioned, physical examination disclosed a conjunctivitis on the side of the lymphadenopathy and the child was referred for ocular consultation on Oct. 25, 1949.

Fig. 1 (Case 1).—Showing unilateral preauricular and submaxillary lymphadenopathy.

Examination disclosed a young child with a slight fever (100° F.) without apparent distress, and a history revealing that she played frequently with her pet cat. The preauricular and submaxillary lymph nodes on the right side were markedly enlarged and slightly tender. (Fig. 1.) No photophobia was present, and discharge was minimal. The most striking feature was the subacute conjunctivitis of the lower fornix and palpebral conjunctiva with several discrete elevated nodular lesions, varying in size from 1 to 5 mm. and all characterized by a central grayish-white area of necrosis. (Fig. 2.)

Laboratory Findings.—The white blood cell count was 11,000 with the differential count showing 10 per cent eosinophiles. The reaction to the tubercu-

lin test was negative. Smears, scrapings, and cultures were negative. A biopsy was taken of the largest nodule which had a focal area of necrosis. The report from the Proctor Laboratory of the University of California School of Medicine revealed the following:

Microscopic Examination.—"The hemotoxylin and eosin sections show a portion of conjunctival membrane which exhibits a very intense inflammation. The epithelial layers show partial destruction with desquamation of the surface

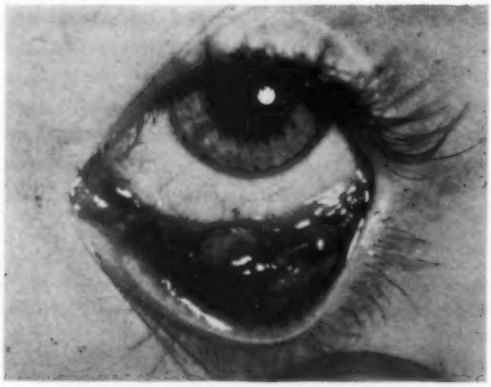

Fig. 2 (Case 1).—Characteristic conjunctival nodular lesions with central grayish-white necrosis.

Fig. 3 (Case 2).—Showing swelling and inflamed semilunar fold with several areas of focal necrosis.

layers and invasion by chronic inflammatory cells. In a few areas there is complete destruction of the epithelium. In the substantia propria there is almost solid infiltration with mononuclear cells, mainly lymphocytes. Occasional epithelioid cells are seen. Only one focal area of necrosis is visible in any of the sections. The Verhoeff Gram stain sections show no fungi which are characteristic of leptothrix. This is also true of regular Gram stains."

Diagnosis.—"Granulomatous conjunctivitis with the histopathological features of leptothricosis."

She was given sulfadiazine systemically and sodium sulfacetimide ophthalmic ointment locally four times daily, and within sixteen days the conjunctival lesion and lymphadenopathy had disappeared.

CASE 2.—R. B., a 6-year-old white boy, reported on Aug. 4, 1949, complaining of a growth in the left eye of three weeks' duration, with only slight irritation and minimal discharge. General physical examination was negative except for a marked left submaxillary and preauricular lymphadenopathy and a temperature of 100° F. History also disclosed that he played with the cat a great deal of the time. The left eye presented a swollen and inflamed semilunar fold in which there were many small areas of focal necrosis, grayish white in appearance. (Fig. 3.) The cornea was clear, and the remainder of the eye examination was negative.

Laboratory Findings.—The white blood cell count was 9,900 with 7 per cent eosinophiles. Smears, cultures, and scrapings were negative. Biopsy was not done because of the semilunar fold involvement and the possibility of a resultant cosmetic blemish.

Sulfadiazine was given systemically with 10 per cent sodium sulfacetimide ointment locally four times daily. Considerable improvement was noted after one week and the process was completely healed five days later.

Fig. 4 (Case 3).—Characteristic conjunctival appearance in a case of leptothricosis conjunctivae; scattered among the follicles are whitish areas of focal necrosis.

The following five cases are from Dr. Phillips Thygeson's files:

CASE 3.—O. P., a 9-year-old Negro boy, reported for an eye examination three days after the onset of a red right eye.

General physical examination was negative except for a temperature of 101° F., and history revealed that the boy slept with his pet cat. Ocular examination revealed a follicular conjunctivitis of the right eye with grossly visible preauricular adenopathy extending to the submaxillary glands. Scattered among the follicles were whitish areas of focal necrosis. (Fig. 4.) Biopsy through a focal necrotic area stained by the Verhoeff Gram stain was positive for leptothrix. (Fig. 5.)

The temperature was normal within ten days, and no suppuration of the glands occurred. The disease slowly regressed over a three-month period.

Fig. 5 (Case 3).—Leptothrix in Parinaud's conjunctivitis.

Fig. 6 (Case 4).—Everted upper tarsus with several focal necrotic areas and transparent pseudomembrane.

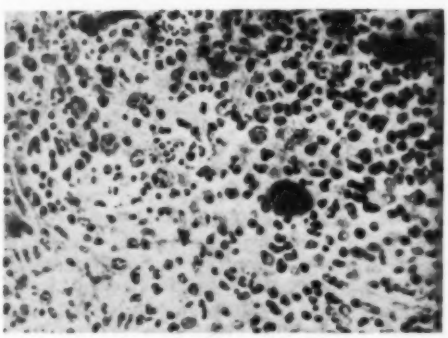

Fig. 7 (Case 4).—Typical histopathology showing numerous macrophages in various stages of necrosis.

CASE 4.—A 15-year-old white girl complained of a red left eye of seven days' duration.

Physical examination was negative except for a low fever for one week (99.6° to 101° F.), and history disclosed that the patient slept with her cat. Ocular examination revealed a conjunctivitis of the left eye with focal areas limited to the upper tarsal conjunctiva. (Fig. 6.) There was no follicular hypertrophy. A transient transparent pseudomembrane over the upper tarsus was evident. The preauricular node on the left was grossly visible but no suppuration of the gland occurred.

Biopsy of a focal necrotic area revealed the presence of leptothrix organisms and characteristic histopathology. (Fig. 7.) It is interesting to note that the leptothrix was also found in smears of the cat's mouth. Slow regression of the disease occurred over a period of two and one-half months.

CASE 5.—C. T., a 13-year-old girl, complained of irritation of the left eye.

Physical examination was negative except for temperature of 99° F. for three days, and history disclosed that there was a cat in the family—though the patient did not sleep with it. Ocular examination showed a conjunctivitis of the left eye which involved the upper fornix primarily. The preauricular lymph node on the left was large and painful, but nonsuppurating. A biopsy was not made. On sulfadiazine therapy systemically, the lesions healed in one week.

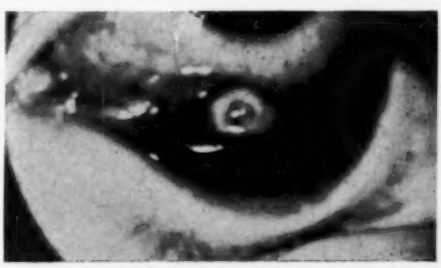

Fig. 8 (Case 6).—Granulomatous conjunctival lesion of inferior fornix.

CASE 6.—R. J., an 11-year-old white girl, complained of a sore right eye of four days' duration.

No fever was present when she was first seen, and examination was negative except for hypertrophy of the lower conjunctival fornix of the right eye. Focal necrotic areas were limited to the lower fornix. (Fig. 8.) She had a grossly visible preauricular node on the right. Smears, scrapings, and cultures were negative. Ground up conjunctival material injected into a rabbit subconjunctivally was negative, and intracerebral injection in mice was also negative. This child's history also revealed that she frequently played with a pet cat.

The lesions failed to respond to therapy with penicillin 300,000 units intramuscularly daily for one week, but cleared in six days on sulfadiazine systemically.

CASE 7.—R. Y., a 17-year-old boy, reported April 29, 1948, complaining of a foreign body sensation in his left eye of seven days' duration.

Examination revealed grossly visible preauricular and submaxillary lymph nodes. Ocular examination was negative except for marked hypertrophy of the palpebral conjunctiva on the left. (Fig. 9.) There were numerous focal necrotic areas on the conjunctiva. Smears, scrapings, and cultures were nega-

tive. Ground up conjunctival material injected subconjunctivally into a rabbit was negative. This material injected intraperitoneally in a guinea pig and mice was also negative, and gave negative results when placed on egg chorioallantoic membrane. The patient's condition improved rapidly in two weeks on sulfadiazine systemically.

Fig. 9 (Case 7).—Marked hypertrophy of inferior fornix and inferior palpebral conjunctiva with many small focal necrotic zones.

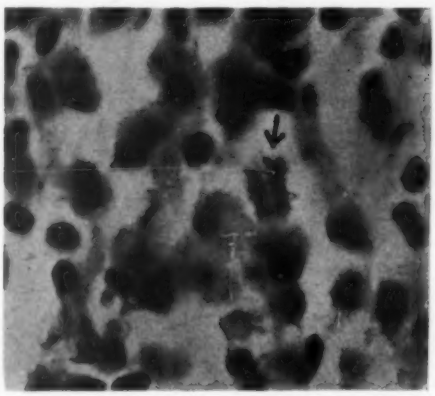

Fig. 10 (Case 8).—Photomicrograph showing a colony of leptothrix in Parinaud's conjunctivitis.

CASE 8 (Case of Dr. John C. Poore).—Mrs. M. P., a 72-year-old white woman, consulted Dr. John C. Poore on Feb. 8, 1950, with the history of the right eye being swollen with mucous discharge causing the eyelids to stick together, of three weeks' duration. A slight temperature was present, which varied from 99° F. to 99.6° F., and it was revealed that the patient had two kittens with which she frequently played. Upon examination, there was a large, tender preauricular lymph node and elevated cervical node on the right, with a conjunctivitis of the right eye. The predominant involvement was in the superior fornix where the conjunctiva was quite edematous and injected, with several follicles at the superior edge of the tarsus. The cornea was normal.

Laboratory Findings.—The white blood cell count was 5,300 with 3 per cent eosinophiles. Kline and Kolmer tests were negative. Agglutination tests for brucellosis and tularemia were negative. Chest x-ray was negative. Smears, scrapings, and cultures were negative. A report from the Proctor Laboratory of the University of California revealed the following:

Microscopic Examination.—"Hematoxylin and eosin sections show a portion of conjunctiva which exhibits a diffuse acute inflammation. On the deeper side a portion of what appears to be tarsus is present and this structure shows considerable inflammation. On the mucosal side most of the epithelium has been destroyed or is infiltrated with polymorphonuclear leucocytes. The substantia propria of the conjunctiva shows an infiltration of polymorphonuclear leucocytes, chronic inflammation, macrophages, and a fair number of eosinophiles. No parasites can be seen in the hematoxylin and eosin sections. The Verhoeff Gram stain shows one colony of leptothrix." (Fig. 10.)

Diagnosis.—"Leptothricosis conjunctivae."

She was given sulfadiazine systemically and 30 per cent sodium sulfacetimide solution locally, and the conjunctival lesions subsided within two weeks. However, the preauricular lymphadenopathy required local incision and drainage. The process completely subsided by March 27, 1950, seven weeks after the patient was first seen.

DISCUSSION

A review of the eight cases presented of oculoglandular conjunctivitis due to leptothricosis reveals several interesting phenomena. Seven of the subjects gave a history of exposure to cats—two of the patients slept with their cats, with leptothrix isolated from the cat's mouth in one case. This would indicate that the source of infection is probably from cats, and might explain the common occurrence in young children. Eosinophilia was present in two of the cases. Characteristically, the conjunctival lesions display several focal necrotic areas, grayish white in appearance.

Isolation of the organism on culture plates is very difficult, and it should be borne in mind that a negative report from the laboratory does not necessarily exclude the diagnosis of leptothricosis. Biopsy examination requires the special technique as described by Verhoeff and one must examine a focal necrotic area in order to demonstrate a leptothrix. Three of the eight cases revealed the presence of a leptothrix. Although the organism cannot always be demonstrated, there is a characteristic histological picture.

Heretofore the treatment was simple excision of the necrotic area, but the use of sulfonamides appears of value in shortening the course of the disease. Five of the eight cases treated with sulfadiazine showed subsidence of the condition in seven to fourteen days, whereas two cases treated with simple excision required two and one-half to three months to regress.

CONCLUSIONS

Leptothricosis conjunctivae, the most common cause of Parinaud's oculoglandular syndrome, is characterized by the following:

1. A unilateral granulomatous conjunctivitis with a grossly visible preauricular and submaxillary lymphadenopathy.

2. Focal necrotic areas in the involved conjunctiva.

3. Possible low-grade fever and eosinophilia.
4. History of exposure to cats.
5. Laboratory confirmation difficult.
6. The value of sulfonamides in shortening the course of the disease.

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THE ROLE OF THE LABORATORY IN ANTIBIOTIC THERAPY

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ANTIBIOTIC agents are among the most frequently used drugs in present-day medicine. They are administered often haphazardly and without clear-cut indication. The great efficacy of accepted antibiotics in controlling infections and their over-all lack of serious toxicity has led many physicians to abandon specific etiologic diagnosis by bacteriological methods. It has become common practice in febrile illnesses to give one antibiotic drug, then, in the absence of a favorable response, to try another, or perhaps even a third, rather than to attempt identification of a responsible organism and direct therapy specifically against it. As more and more good antibiotic agents become available, it is tempting to use not one, but three or four different agents simultaneously. The possible effects of such "shotgun" therapy are largely unknown at present. In view of these trends it may be in order to evaluate the proper place of the laboratory in antibiotic therapy, and point out some possible ill effects of the indiscriminate use of antibiotics.

In the field of chemotherapy the laboratory serves two main functions: fundamental research and guidance of therapy. In the development of any new chemotherapeutic agent the research aspects include not only the actual production, isolation, and purification of the substance but also its pharmacological and toxicological characterization, determination of its antimicrobial spectrum, etc. In the clinical investigation of such a new chemotherapeutic agent, objective laboratory determinations of drug absorption, excretion, levels in body fluids, and effects on microbial populations are naturally paramount.

When a drug reaches the market, the laboratory, for some time, continues to be important in the guidance of therapy. As clinical experience with a given drug accumulates, there appears to be less and less need for complete laboratory control of therapy. Soon the drug is used largely on an empirical basis: it is applied to control symptoms rather than to combat specific infective agents determined by laboratory diagnosis. Diagnostic procedures are resorted to frequently not when the patient first presents his problem, but when drugs have failed to solve it.

From the standpoint of rational therapy and "scientific medicine" this trend is obviously undesirable. In addition, neglecting specific etiological diagnosis in infectious disease may well be detrimental to the patient, and make the management of the illness more difficult.

The laboratory can aid in the rational guidance of chemotherapy in the following ways:

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1. The microorganisms involved in the infectious process can be determined, and in some specific instances also their approximate number in blood, urine, etc.

2. The "sensitivity" of the microorganism isolated from the patient to the drug used for therapy can be estimated. Routine determinations usually indicate the minimum concentration of the chemotherapeutic agent necessary to inhibit growth. In some instances it may be desirable to establish also the minimum amount necessary to *kill* microorganisms in the test tube.

3. The "level" of drug in the body fluids or excretions of a patient under treatment may be measured. In the routine use of well-established drugs this is rarely necessary. In some patients presenting special problems of infection it may be helpful.

4. In the case of infections with notoriously resistant microorganisms it may be indicated to evaluate the combined action of several chemotherapeutic agents in the test tube before administering them to the patient.

5. Standard clinical laboratory procedures often offer the best guidance for early detection of drug toxicity, of the control or relapse of infection, etc.

It is evident to every clinician that it is neither necessary nor desirable to use such laboratory procedures in every case prior to starting antibiotic therapy. This paper points out some of the positive indications and reasons for laboratory determinations. Case reports illustrate the benefits of using laboratory procedures when indicated and the possible detriment to the patient of failing to do so.

Reasons for laboratory procedures may be placed under two broad headings:

A. Some examinations are positively helpful in the management of the patient, yielding results that are directly contributory for the planning of therapy.

B. Certain laboratory examinations may safeguard against possible damage resulting from the indiscriminate use of antibiotics without the proper indications, i.e., "shotgun therapy."

A. POSITIVE GAIN FROM LABORATORY EXAMINATIONS

"The cost of bacteriological diagnosis is excessive—we want to save the patient money," is a frequent objection to laboratory tests. It is true that thorough bacteriological investigation is often expensive. However, in terms of the cost of prolonged therapy with antibiotics the expenditure for laboratory examinations is negligible. Much more important is the possible serious damage to the patient that may result from inadequate or improper chemotherapy. The following case illustrates such a problem.

CASE 1.—E. W., a 59-year-old postal clerk, in February, 1948, noticed a hard, painless swelling on the left side of his neck, which increased slowly in size. Shortly thereafter he developed an afternoon fever and began losing weight. A biopsy indicated "chronic inflammation." No tissue was submitted for bacteriological examination. The biopsy site failed to heal, with pus draining from a shallow sinus. Local x-ray therapy, and penicillin, had no effect. The clinical impression was "tuberculous adenitis." In July, 1948, extensive laboratory investigation, including bacteriological cultures from the draining sinus were noncontributory. A second biopsy indicated a "subacute granuloma" histologically, but again no tissue was examined bacteriologically. The

patient was treated with 2.4 million units of penicillin daily, which resulted in some lowering of his daily afternoon temperature, but his weight loss continued. A third biopsy was taken on July 22, 1948. Results of pathological examination were the same as before, but inoculation of ground tissue into guinea pigs resulted in the recovery of tubercle bacilli. By the time the diagnosis was established the process had disseminated, and miliary lung lesions were observed in chest x-rays. The patient was placed in a sanatorium, and subjected to repeated courses of streptomycin therapy before any definite improvement could be observed.

Comment.—Had the proper laboratory examination (culture and guinea pig inoculation of ground tissue from biopsy) been performed at the patient's first visit, it is probable that a great deal of suffering, serious organic damage, and the needless expenditure of large sums of money could have been avoided. To perform indicated laboratory procedures is likely to save rather than to waste, in all respects.

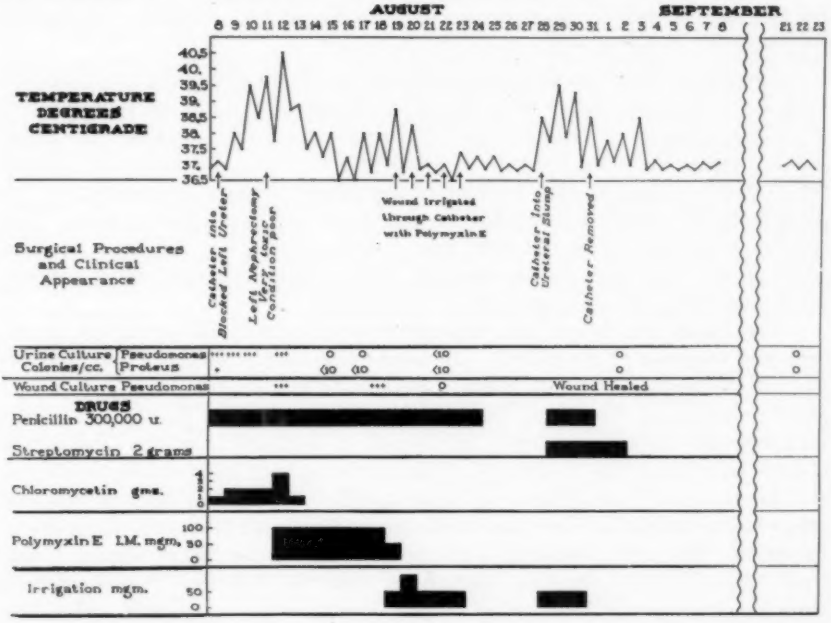

Chart 1.

Of the satisfactory antibiotic drugs now available, several have broad antimicrobial spectra. In many infections it matters little whether one or the other antibiotic is employed. In some difficult cases, however, it is of vital importance to determine the most effective antibiotic by laboratory examination. Treatment of a desperately ill patient with a drug especially suited to his condition may then be life-saving.

CASE 2. (Chart 1).—S. S., a 32-year-old housewife, suffered from increasing pain in the left flank and back and slight fever for several months. Urological

study indicated a left pyelonephritis and a blocked ureter. Catheterization of the left ureter on Aug. 8, 1949, yielded pus. Laboratory examination showed a pure culture of *Pseudomonas aeruginosa,* resistant to all common antibiotics but highly susceptible to polymyxin E. In spite of prophylactic penicillin and Chloromycetin, there was high fever and a positive urine culture. A left nephrectomy was performed on August 11. Due to the patient's critical condition only part of the left ureter could be resected. The patient was still critically ill, when, twenty-four hours later, polymyxin E was started. Promptly the temperature came down to normal and the urine cultures were negative. Aside from a mild drug reaction (including drug fever, and central nervous system symptoms), the patient felt well. The nephrectomy wound, however, continued to be infected with *Ps. aeruginosa.* Local irrigation with solutions of polymyxin (1 mg./ml.) promptly and permanently eradicated the infection, and the wound healed rapidly. Urine cultures showed the presence of few *Ps. aeruginosa* and Proteus organisms, probably residing in the ureteral stump. The Proteus was found highly susceptible to streptomycin. Local irrigation of the stump with polymyxin solutions and systemic administration of streptomycin for five days completely and permanently eradicated the infection. The patient subsequently remained well.

Comment.—This patient was moribund due to an overwhelming infection with *Ps. aeruginosa,* which was resistant to streptomycin and not influenced by the administration of penicillin and Chloromycetin. The organism was found highly susceptible in the test tube to polymyxin E, a drug not generally accepted for systemic administration because of significant toxicity. However, in this desperately ill patient polymyxin was chosen as the "most effective agent," and proved to be life-saving. It later was instrumental in eradicating a residual focus of infection with *Ps. aeruginosa.* With proper management of therapy, toxic manifestations were temporary and minimal.

The dosage schedule of an antibiotic is based principally on clinical experience and response of the patient. In some instances the test tube sensitivity of the culture isolated from the patient serves as a guide. Only rarely it is indicated to determine "levels" of the drug in the patient's body fluids. Blood level measurements have been largely abandoned in antibiotic therapy since it was clearly recognized that antibiotic action in tissues was independent of demonstrable amounts of the drug in the blood stream.[6, 7, 11] Infectious processes that take place principally within the blood stream, e.g., bacterial endocarditis, are an exception. There the blood level of one antibiotic is significant because it pictures the amount of drug having contact with the infecting microorganisms. Both sensitivity and blood level determinations are consequently helpful in adjusting the dosage schedule.

CASE 3.—J. B., a 35-year-old engineer, had known for many years that he had a coarctation of the aorta, but had suffered from very little disability. In July, 1948, he noticed increasing malaise, fever, and weakness. Blood cultures are said to have yielded "staphylococci." He was treated with streptomycin, aureomycin (4 to 6 Gm. daily), and penicillin (600,000 units daily) for two weeks. Subsequent blood cultures were positive for "alpha hemolytic streptococci." The patient was hospitalized and given penicillin (10,000,000 units daily) for four weeks. Blood cultures were negative at the end of therapy but symptoms returned in four weeks and blood cultures again grew a *"Streptococcus viridans,"* which was inhibited by 0.75 unit/ml. penicillin. The patient

was treated with penicillin (25,000,000 units daily) for seven weeks. During therapy, blood levels were estimated at 0.8 unit/ml. penicillin, and cultures were negative until treatment was stopped. Subsequently, they again showed "few *Streptococcus viridans*." After these three therapeutic failures, the patient was admitted to the University of California Hospital in November, 1949. He showed signs of aortic coarctation. His spleen was enlarged, there were petechiae and splinter hemorrhages, and he had a daily temperature spike, up to 38.0° C. Blood cultures grew a *Streptococcus viridans* which was inhibited by penicillin 5.0 units/ml. The organism was shown to survive in 25 units/ml. for fourty-eight hours, but was killed on exposure to 50.0 units/ml. Administration of penicillin, 25,000,000 units daily, failed to yield satisfactory blood levels and the fever continued. Consequently the patient was placed on a daily dose of penicillin, 50,000,000 units, caronamide, 24 Gm., aureomycin, 2 Gm., and dihydrostreptomycin, 2 Gm. This course was continued for six weeks. All cultures during and after this treatment remained sterile. Follow-up examination four months after cessation of therapy indicated that blood cultures were negative and the patient continued to be well.

Comment.—A review of this case suggests strongly that repeated inadequate courses of chemotherapy failed to eradicate the infection and permitted the etiological organisms to develop an unusual degree of antibiotic resistance. Ultimate cure was obtained when the very large doses of penicillin were given which laboratory examinations had indicated. This case also illustrates the occasional need for special laboratory tests: it was essential to determine the amount of penicillin necessary to *kill* all exposed microorganisms[8] in vitro, not only to inhibit their growth. Therapeutic doses of penicillin and caronamide based on bactericidal rather than bacteriostatic concentrations of penicillin in vitro succeeded in eradicating the infection. The possible contribution made by aureomycin and dihydrostreptomycin toward the cure in this case remains uncertain.

In certain infectious processes single antibiotic agents fail, whereas suitable combinations achieve a cure. Haphazard mixtures of antibiotics may not only be ineffective and wasteful but occasionally harmful (see below). Laboratory assay of the joint action of several antibiotics on the infecting organisms can provide specific guidance for combined chemotherapy.

Case 4.—F. A., a 63-year-old man, underwent a ureteral transplant operation following other surgical procedures on the urinary tract. His postoperative course was uneventful except for the persistence of a narrow sinus in the left lower quadrant from which purulent material drained constantly. The patient received penicillin, streptomycin, aureomycin, and Chloromycetin over a period of four weeks, but the sinus failed to heal. Cultures from the drainage revealed enterococci, *Ps. aeruginosa*, and Proteus. These organisms were resistant to all antibiotics tested singly, but were completely inhibited by mixtures of bacitracin and polymyxin. When mixtures of these two drugs were applied topically (bacitracin, 1,000 units/ml., polymyxin, 1 mg./ml.), the infection was cleared rapidly, and the sinus closed in eight days.

Comment.—In this case the therapeutic armamentarium had been nearly exhausted in prolonged attempts to eradicate the infection in the sinus tract and permit its healing. All common antibiotics had previously been employed. They had removed most of the susceptible bacteria, leaving only three resistant

varieties. The combination of two uncommonly used drugs, bacitracin and polymyxin, was found highly effective against these organisms in vitro. Subsequent prompt clinical healing substantiated this impression.

CASE 5 (Chart 2).—J. E., a 74-year-old laborer, had suffered from increasing prostatism for three months, with urinary frequency, hesitancy, incontinence. He entered the hospital when unable to void for twenty-four hours. Examination revealed a well-nourished, afebrile, healthy appearing man. His prostate was hard, nodular, much enlarged, and fixed. X-rays indicated lung metastases from a probable prostatic carcinoma. Since radical prostatectomy was impossible because of the spread of the neoplasm, a palliative transurethral resection was performed. No preoperative urine culture was obtained, but prophylactic penicillin (600,000 units daily) was administered. After surgery the patient developed a high fever and the picture of general sepsis. Two blood cultures were positive for enterococci. The patient was comatose and appeared moribund. Chloromycetin and streptomycin were ineffective. The enterococci were inhibited in vitro by mixtures of penicillin and streptomycin. The patient was therefore started on combined therapy with penicillin (4,800,000 units daily) and dihydrostreptomycin (2.0 Gm. daily). There was rapid defervescence and all subsequent blood cultures remained sterile. The patient improved rapidly and was discharged in eleven days, cured of the systemic infection.

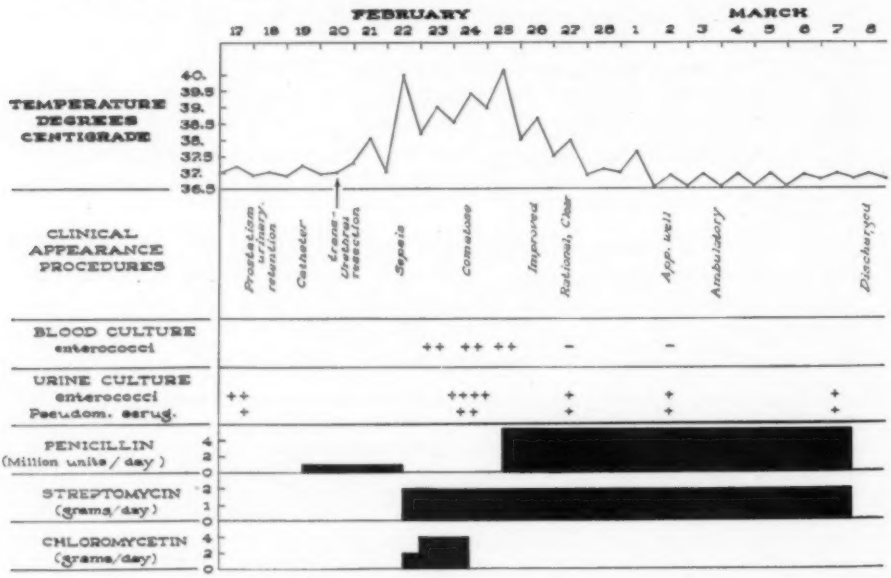

Chart 2.

Comment.—This patient undoubtedly had a mild urinary tract infection with enterococci when he underwent operation. Moderate doses of penicillin did not prevent the organisms from reaching the blood stream during operation and subsequently producing sepsis. Streptomycin and Chloromycetin when used alone also failed to suppress the infection. Only when the effec-

tive combination penicillin plus streptomycin was administered a dramatic recovery ensued, with prompt sterilization of the blood stream. It seems probable that the postoperative complications could have been prevented if preoperative urine cultures had been obtained, enterococcal infection demonstrated, and adequate prophylaxis with penicillin plus streptomycin instituted.

B. SAFEGUARDING AGAINST POSSIBLE HARM OF "SHOTGUN THERAPY" WITH ANTIBIOTICS

Most accepted antibiotics are relatively nontoxic drugs. Nevertheless, some undesirable side actions can and do occur frequently. In addition to drug toxicity, sensitivity reactions to many antibiotic agents are common. When administration of a drug is essential the side actions naturally are accepted, but the physician should be certain of the proper indication and need for the drug. Laboratory tests often establish or confirm the indication for a certain antibiotic and help to avoid subjecting the patient unnecessarily to reactions of toxicity or sensitivity.

All microbial populations contain mutants that are relatively resistant to antibiotics. Repeated or prolonged exposure of such a population to a given drug results in a selection of resistant forms: The antibiotic-sensitive organisms are eliminated, and the resistant ones take their place. As a result, resistant "strains" of organisms develop and increase in frequency. Such is the case with staphylococci and penicillin. Prior to the widespread and often indiscriminate use of penicillin, most strains of staphylococci were relatively susceptible to the drug. Recently[3, 4, 5, 13] the majority of strains isolated in hospitals are highly penicillin-resistant. The problem created by this development is illustrated by the following case.

CASE 6.—J. H., a 38-year-old man, suffered from joint pains, tiredness, chills, fever, and weight loss for several months before entering the hospital in June, 1948. He was studied extensively and the final diagnosis was aplastic anemia, etiology unknown. He was given several transfusions and discharged after a hospital stay of three weeks. A few days after his discharge he developed a boil above the left ear. Shortly thereafter he bruised his hand and developed marked swelling, cellulitis, and lymphadenitis. An abscess developed in the palmar spaces and was drained. Cultures from the pus revealed a coagulase-positive hemolytic *Staphylococcus aureus,* inhibited in vitro by penicillin 5.0 units/ml. Examination of the blood indicated marked anemia, leucopenia (400 W.B.C./cm.), and granulopenia (30 per cent polymorphonuclears). The patient was intensively treated with penicillin, 15,000,000 units daily, full doses of sulfadiazine, transfusions, and parenteral fluids. Nevertheless he ran a downhill course and died in eleven days. An autopsy revealed peritonitis and multiple abscesses in both lungs. From these lesions hemolytic staphylococci were cultured that had the same sensitivity (inhibited by 5.0 units/ml. penicillin) as the staphylococci cultured prior to treatment.

Comment.—Similar widespread development of resistance of microorganisms to streptomycin has taken place and is likely to occur to a greater or lesser extent with other antibiotics. Consequently, it would seem wise to interfere with this process of selection as much as possible by using antibiotics sparingly and only when necessary.

Striking changes can be observed in the normal flora of the human body as a consequence of exposure to antibiotics, particularly those with a narrow antibacterial spectrum. Such agents tend to suppress susceptible members of the normal flora and permit the unrestricted development of nonsusceptible microbial varieties. This creates an "imbalance" in the flora which may sometimes lead to the production of disease. The following case shows such a development.

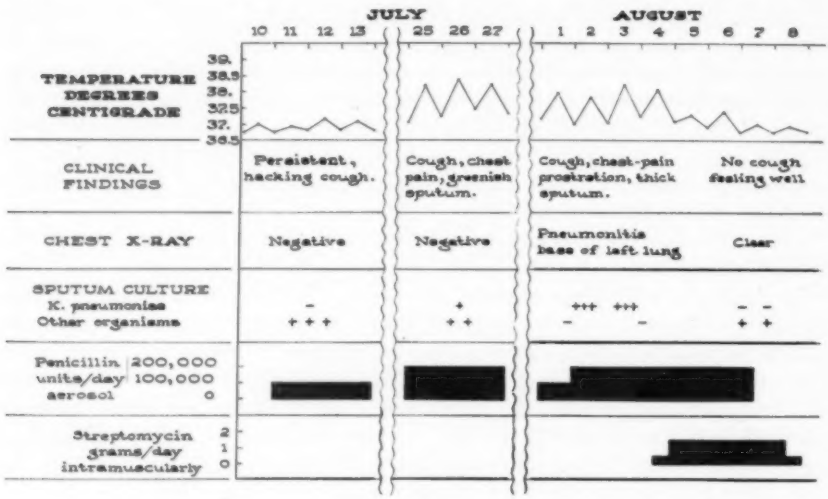

Chart 3.

CASE 7 (Chart 3).—C. R., a 70-year-old man, had known for over eighteen years that he suffered from pernicious anemia but he took liver preparations only irregularly. For several months before admission to the hospital he noted increasing weakness and unsteadiness, and also intermittent cough, for which he used a "penicillin inhaler" with some improvement. Later, he developed more cough, with "greenish" sputum, and some fever. On admission to the hospital he was seen to be weak, pale, white-haired and blue-eyed, with blood and bone marrow findings characteristic of pernicious anemia, and some evidence of combined sclerosis. He was started on parenteral liver therapy. His cough and slight daily fever continued, but a chest x-ray was entirely negative and sputum cultures showed only a few Klebsiella colonies. He again was given penicillin aerosol (200,000 units daily) but without response. A few days later a chest x-ray indicated pneumonitis at the base of the left lung and sputum cultures yielded a pure growth of *Klebsiella pneumoniae*, which was sensitive to streptomycin, 1 mg./ml. Parenteral streptomycin therapy promptly cured him of the Friedländer's infection.

Comment.—Similar incidents may arise from the indiscriminate use of antibiotics. In the same category are infections due to two or more organisms in which treatment is directed inadvertently against only one. Painstaking laboratory examination can usually obviate this difficulty.[1, 14, 15]

The normal flora of the human body has some important functions, e.g., the synthesis of vitamins by intestinal organisms. Complete suppression of the intestinal flora by chemotherapeutic agents under certain circumstances can give rise to serious deficiencies, as shown in the following case.

CASE 8.—M. I., a 24-year-old housewife, developed meningitis due to *Hemophilus influenzae* in March, 1949. She was treated with streptomycin, sulfadiazine, and penicillin for ten days, with good response. Meningitis recurred in April and June, 1949, and responded to similar treatment. In the course of these attacks endocrine abnormalities became apparent, as well as bitemporal hemianopsia and enlargement of the sella turcica, suggestive of a pituitary tumor. In September, 1949, the patient again developed nausea, vomiting, confusion, and fever. Her spinal fluid showed high protein, high cell count, and low sugar (23 mg. per cent). Although the culture was again negative, a recurrence of meningitis was diagnosed and intensive antibiotic therapy started. She received daily penicillin, 1 to 2.4 million units, dihydrostreptomycin, 4.0 Gm., aureomycin 1.5 Gm., and Chloromycetin 1.0 Gm. The patient's food intake was very poor and she was maintained largely by parenteral fluids. After two weeks on the antibiotic regimen, ecchymotic spots appeared at the sites of injection; the prothrombin level was found to be 23 per cent of normal. She received 50 mg. of parenteral vitamin K which resulted in a prompt rise of the prothrombin level to 108 per cent. Four days later the patient suddenly went into shock from an intestinal hemorrhage. In spite of several blood transfusions and 10 mg. of parenteral vitamin K daily, the prothrombin levels continued to be low (66 per cent of normal) for four days. Subsequently, parenteral vitamin K therapy was continued until the massive chemotherapy could be stopped. Ultimately, the patient recovered sufficiently from the infection to have a craniotomy; exploration of a craniopharyngioma revealed an abscess which had evidently been the source of the repeated meningitic infections.

Comment.—This patient was unable to take much food by mouth and was maintained largely by parenteral means. No supplementary vitamins were administered. Consequently she developed a severe prothrombin deficiency and hemorrhagic disease when her intestinal flora, suppressed by massive chemotherapy, was unable to manufacture vitamin K. Such instances are probably rare, but indicate the need for laboratory control of combined antibiotic treatment.

It has been shown in a number of infections that simultaneous therapy with several drugs is effective although each drug alone fails to cure. Some experimental evidence points to true synergism between antibiotics,[2, 8, 9, 12] while other evidence has demonstrated apparent antagonism between some antibiotics,[9, 10] It is quite possible that similar phenomena may be encountered when several antibiotics are administered simultaneously in human disease. If that were so the physician would be neutralizing, instead of potentiating, the action of one antibiotic agent by another. Until more complete knowledge on the effects of combined antibiotic therapy is acquired, guidance by laboratory tests is necessary.

CONCLUSIONS

To safeguard the best interests of the patient, the physician must know the proper indications for essential laboratory procedures in rational anti-

biotic therapy. He must be aware of the fact that haphazard administration of antibiotic agents may produce serious damage which can be prevented by utilizing the information obtainable from intelligent use of laboratory examinations.

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A NOTE ON THE PSYCHOLOGICAL IMPLICATIONS OF THUMB-SUCKING

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THUMB-SUCKING is one of the most common forms of oral activity in children with which the pediatrician is confronted. It is also probable that this persists for a longer time in many children than any other type of behavior about which parents become anxious. It may occur as an isolated symptom, but more frequently it is associated with problems in feeding, toilet training, or general behavior. In this child-oriented period of our society, parents often anxiously inquire about the significance of thumb-sucking in the personality development of their children. In addition to this, there is also concern as to the influence of thumb-sucking upon the formation of the facial features of the child, especially its influence upon the development of the jaws. On this score, the dentist is drawn into the picture, and is confronted by the anxious parents with similar questions. As a result, there has been a great deal of discussion within and between the skills of pediatrics, dentistry, and psychiatry about the etiology, prognosis, and therapy of this form of behavior in children. It might be added that these discussions have not always been dispassionate, and rather diverse viewpoints regarding etiology and treatment are often heatedly presented.

One is tempted to speculate regarding the extent to which social attitudes toward self-gratification current at any given period in the history of a culture influence the "scientific" ideas and opinions expressed about thumb-sucking. It does not require much exploration to learn that the attitudes toward thumb-sucking vary in different cultures and have varied rather markedly even in the past two or three generations in our own culture. At one time, thumb-sucking was looked upon rather indulgently, and the oral activity was even encouraged by the provision of pacifiers. At another period, thumb-sucking was frowned upon and felt to be an activity detrimental to the physical and psychological development of the child. At the present time, there seems to be a sharper conflict between these two viewpoints, with a tendency to gravitate toward the earlier viewpoint of indulging, or at least not prohibiting, the activity.

Without pursuing this aspect of the problem any further, we can state that current interest in thumb-sucking has centered around the following points: (1) its influence upon the physical development of the child; (2) the significance of thumb-sucking as a manifestation of the child's psychological development. In this paper I would like to outline briefly the biological basis of thumb-sucking and its psychological implications.

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There may be a great deal of disagreement regarding everything else, but there would be almost universal agreement that sucking is probably the most important volitional motor activity of the newborn infant. This is the one patterned activity present at birth, perhaps even before birth, and the absence of which after birth will cause a great deal of concern to all those interested in the infant. It would probably be granted by all of us that the infant's survival depends upon his ability to suck, since it is through this function that he is able to ingest food. On the occasions where the sucking mechanism has not become established, all sorts of methods are utilized to stimulate its development so that it will be adequate to the ingestion of sufficient quantities of food. Since sucking serves this function in the life of the infant, it is reasonable to state that it is an expression of a basic impulse, the instinct to self-preservation. This consideration establishes at the same time a fundamental psychological implication of sucking and demonstrates the inseparable unity of biological and psychological phenomena.

The mucocutaneous junctions are the most sensitive areas on the body surface. Pleasurable and painful stimuli are most keenly felt in such areas. This is notably true early in life of the oral area, and in addition many complicated activities usually involving the participation of other people and essential both for the survival of the organism as well as its comfort and pleasure center around this area. During the first months of life, the infant obtains his greatest pleasurable sensations by means of the oral area. This is associated with other pleasurable sensations obtained from being held, fondled, and spoken to in preparation for and during the nursing process. It has been observed that in many instances sucking movements will continue long after there has been an ample ingestion of food. It would seem that sucking also occurs in response to a second impulse tending toward the satisfaction of another need. This can be described as a need for sensual gratification and that, associated with its satisfaction, the infant can be inferred to experience a sensation of pleasure. This has been inferred, not only by the observation of infants, but also from the expressions, verbal and otherwise, of children past the stage of infancy. The need for sensual gratification is intimately connected with, and tends to reinforce, the instinct for self-preservation, but continues to operate independently as well.

Through the observation of infants, it has also been shown that, where the need to suck has somehow been made difficult or even prevented by disease or other factors, one finds rather striking psychological manifestations, such as irritability, restlessness, excessive crying, and, in extreme instances, apathy and listlessness.

Observations by Gesell and others have described a hand-to-mouth pattern characteristic of all infants. In the many random movements that an infant makes with its limbs, he quickly establishes this hand-to-mouth pattern. At this early period, it would seem as if the oral zone serves not only for the ingestion of food or for sensual gratifications, but also for the exploration of the nature of readily movable objects in his environment. The purpose of this would seem to be the determination of their edibility or pleasure-giving potentialities. At least in part, the infant seems to explore his world by means of

the sensations of the oral area. We could reasonably postulate that here we may have the primitive manifestations of curiosity and therefore the basis for learning. The infant soon learns that he can most easily obtain sensual gratification through sucking his thumb. To some extent this serves to make him independent of others in obtaining pleasure. If we then remember how helpless the infant is and how his entire security system revolves around the mouth, we can begin to understand the manifold psychological reactions which stem from this fact. His satisfactions are intimately tied up with, and are dependent upon, another person, the mother. The earliest pattern of his relationship to the mother is established mainly around oral activities. The earliest satisfactions and frustrations experienced in relation to the mother center chiefly around this area of the body. We can thus begin to understand the significance of oral activity in the establishment of important patterns of interpersonal relations. The awareness that satisfaction can be obtained from his own body, i.e., sucking his thumb, is an important element in these patterns. In the psychological development of the individual we can trace this impulse in ostensibly quite different manifestations in later life. The sensual gratification or pleasure that the infant obtains through nursing or through sucking its thumb is the same form of energy which, as it develops and changes through the growth of the child, finally becomes manifest in what we can clearly recognize as the sexual impulse. The need for sensual gratification is no different in quality, whether it expresses itself in thumb-sucking in the infant or child or whether it is expressed in the genital activity of the adolescent and adult.

When needs of whatever nature are frustrated or inadequately met, all individuals tend to react with anxiety. In addition to the many maneuvers through which he attempts to overcome this uncomfortable feeling, the individual will also tend to adopt old, familiar, but outgrown patterns of behavior. These may be patterns which have previously succeeded in diminishing or abolishing anxiety. When these patterns are not in accord with the individual's current state of biological maturity and the requirements of the culture, we call them regressive forms of behavior, and the phenomenon is called regression. Sucking is one of the earliest patterns of behavior and perhaps the one most firmly established. Since the child has already learned during infancy that he can obtain through his own body some of the pleasures to be derived from sucking, he will frequently resume thumb-sucking during periods when, for whatever reason, he feels an increased amount of anxiety.

The significance of thumb-sucking as an indication of psychopathology may be described further from two important aspects of this activity. It is a means of obtaining sensual gratification at an age when the "normal" child (probably meaning the majority) has relegated this activity to the background and only rarely, if ever, indulges in it. At the same time, this gratification is obtained by means of a part of his own body. This latter consideration may have the most important implications psychologically.

Up to this point we have been discussing thumb-sucking mainly as a normal manifestation of basic drives, but we can no longer evade the question

as to when or under what circumstances it can be regarded as an expression of an emotional disturbance. This is difficult to answer satisfactorily, since there is no single standard by which this is determined. Age would seem to be the most obvious and in many instances the most useful criterion. But the biopsychological development of the organism does not maintain a point-to-point relationship with its chronological experience, and age, therefore, cannot be used too rigidly as a standard. At the same time, we are faced with the fact that thumb-sucking may be symptomatic of emotional disturbances even at an age during which, as I have stated before, it is a normal activity. Even in the very young infant, disturbed for any reason, increased sucking activity can be observed. During ritual circumcision, for example, the infant is often given something to suck on. It might be compared to the increased food intake which occurs in some adults during periods of emotional tension. We are thus faced with a quantitative factor and one which at this point we could not even begin adequately to define. Perhaps we will gain more clarity if we follow the further development of those impulses which obtain their earliest expression through sucking.

The oral area remains the sole location concerned with the ingestion of food, but voluntary oral activities other than sucking begin to assume a role in serving the nutritional needs of the organism before the end of the first year of life. These are biting and chewing, which gradually become more important than sucking in meeting the self-preservative needs of the child. But for some time after sucking has lost its central role in this respect, it still continues to provide the child with a major source of sensual gratification. It should be remembered, however, that this is not the sole source for the satisfaction of this need. It is worth reiterating that the drive for sensual gratification subserves and reinforces activities tending toward the survival and growth of the organism, but at the same time is an end in itself and equally necessary for the survival and growth of the organism. Also it becomes associated with other activities of the organism which culminate in sensual gratification (muscular, intellectual, and sexual activities) and contribute to survival and growth.

The independent activity of this drive is more clearly demonstrated at this point in the child's development when sucking occurs more often quite independently of the intake of food. But even in respect to sensual gratification (it might be equally valid to term it the pleasure drive), the oral area at first shares, and later gradually gives up, its central role to other areas of the body and to other activities. These activities involve the use of the developing sensory and motor apparatus, the operation of which provides the infant with a wider variety of gratifications. We would include here looking, listening, probably smelling, general muscular activity, as well as the gradual acquisition of the many complicated, coordinated movements now becoming possible as a result of the increasing maturation of the nervous system. All these developments utilize a great share of the energy formerly channeled into oral activity and provide the child with sensual gratification formerly obtained in this way.

These maturational events at the same time increase the complexity of the child's interpersonal relations and a great deal of energy is utilized in mastering the intricacies of these relationships.

In addition, the increasing possibility of voluntary control of excretory functions combining with the social pressures now operating mainly through the mother begin to divert the child's attention to other areas of the body covered by mucous membrane, the urethra and anus. With the occurrence of all these events in the child's biological and social experience we can see that two things are happening. On the one hand, the ways and means through which he may obtain satisfaction for his needs are progressively multiplying, but at the same time this very fact makes increasing demands upon the exercise of all those functions which enter into the complex phenomenon we call adjustment. Thus, sucking almost completely ends as a means of meeting the child's nutritional needs, and plays only a minor role in gratifying sensual needs, though it probably never completely disappears (witness smoking and gum chewing). No phase in the development of the organism begins or ends abruptly, nor do developmental phenomena occur in serial order. Periods of human development about which we tend to speak as if they did develop serially really overlap and merge into one another, and we may see the characteristic manifestations of different growth periods at the same time in the same individual. By and large, the importance of sucking begins to decrease by the end of the second year. Thumb-sucking, therefore, begins to diminish about that time and in a large proportion of children is no longer a prominant activity by the end of the third year of life. It would probably be safer to say that this is mainly true in our culture and in this general period of our history. Variations have been reported in other cultures and, as mentioned before, in other periods of our cultural history.

Thus, we can reasonably state that when thumb-sucking persists or recurs at a time when the child is biologically capable of satisfying his basic needs in more complicated ways, in fact, when these needs can only be met satisfactorily by means of these more advanced procedures, it may then be regarded as at least one indication (the one most troublesome to the environment) of the child's difficulty or inability to accept or master the modes of obtaining gratification more in accordance with the biological maturity of his body. It may be useful to note that the complexity of the advanced procedures resides more in the relationships with other people than in the management of his own body.

The other important psychopathological aspect of thumb-sucking is in regard to the means or object through which the child obtains gratification. Because of its originally intimate connection with the self-preservative drive, sensual gratification is obtained through another person, the mother. The intimate association of these two forces or drives and their concentration upon the mother as the object immediately brings another person into relationship with the child, and implicity carries within it the nuclear source of all future interpersonal relationships. All the varieties of human feeling and behavior are probably experienced and expressed by the child in this early relationship

with the mother. What occurs later as the child grows is only the amplification and further elaboration of the basic patterns established at this time. One might use the analogy of the basic musical theme from which the complexities of a symphony are developed. Since in a society the individual can achieve the satisfaction of his needs mainly through or in cooperation with one or more other individuals, all other factors being equal, the established pattern of his interpersonal relationships will determine how adequately he accomplishes this. The persistent thumb-sucker indicates in effect that he is unable to obtain necessary satisfactions by means of his accustomed ways of interreacting with other people, has at least for the time being and to some extent given up his attempts to obtain gratification through and with others, and to this extent has withdrawn within himself. This activity with the associated fantasies can be regarded as the prototype of other forms and even more severe degrees of withdrawal.

When viewed from this background persistent thumb-sucking can no longer be considered apart from the emotional state of the child, which necessarily demands a consideration of his relationship with people significant to him. The focus of our attention must then change and, instead of regarding thumb-sucking as if it were a disease, we must see it as a symptom, perhaps only one among others, which indicates an emotional disturbance or in other words a disturbance in interpersonal relations. Though this view may seem to complicate matters, it really makes the problem more comprehensible and leads to a therapeutic approach based upon etiology.

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STUDIES ON THE ETIOLOGY OF EXANTHEMA SUBITUM (ROSEOLA INFANTUM)

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THERE are many reasons why the etiology, method of transmission, and mechanism of infection of exanthema subitum are worthy of study. Until the present time, in contrast to all of the other common exanthemas, the production of this disease by the actual transmission of an infectious agent has not been conclusively demonstrated.

The disease was described by Meigs and Pepper in a textbook written in 1870. Their description corresponds closely with that of subsequent authors although they doubtless included some of the other mild exanthemas among their cases. However, it is worthy of note that even older textbooks refer to roseola in infancy and apparently recognition of this disease as a syndrome of infancy existed fully a century ago. Interest was revived by a paper by Zahorsky in 1910[1] and of Veeder[2] in 1918 and subsequent papers have done little except to emphasize the frequency of this disease and to define it as a definite symptom complex and, in all probability, a disease entity. The recent paper of Berenberg and collaborators[3] gives a complete résumé of these clinical reports.

The disease picture is well known. The infection is extremely common and has become relatively more frequent with the decline in the incidence of many other common infections. The onset of fever is often abrupt and is accompanied by mild evidences of illness although occasionally the sudden high fever may provoke a convulsion. The fever is continuously or irregularly high for about three days and then drops, usually precipitately, to characteristically subnormal levels. The typical eruption appears after the decline of the temperature and is commonly most marked twelve hours thereafter.

During the febrile period examination reveals little. There is some redness of the tonsils and pharynx and rarely there is a little filmy white tonsillar exudate. The suboccipital glands are palpably enlarged, especially on the second and third days of the fever, but not as large nor as tender as in rubella. Other superficial glands and the spleen are not demonstrably enlarged. Other findings are entirely normal. The typical, pale pink, finely macular rose rash is easily recognized if looked for at the proper time but otherwise frequently passes unnoted, especially if it is present at night. The eruption appears be-

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hind the ears, frequently spares the face, scatters down the trunk to be most prominent over the thighs and buttocks where each macule may be surrounded by a pale halo.

The white blood count shows a steady decline during the three days of fever, sometimes reaching a considerable leucopenia, but rapidly returning to normal after the eruption appears. Other laboratory findings are negative.

There are no reported fatalities and serious sequelae are virtually nonexistant. Fever and slight irritability are almost the only symptoms except that a convulsion may accompany the abrupt rise of fever. The general well-being of the child with high fever helps to differentiate this infection.

Interest in this disease stems from the following considerations:

1. Children between the ages of 6 months and 2 years are almost exclusively affected. This period of life represents the lowest ebb in the immune status of the individual. A very few cases have been described in older children and adults but these instances so depart from usual experience as to suggest that they may be due to confusion with some other disease. The relative insusceptibility to many infections which is present under the age of 6 months, whether this represents specific transplacental protection or simply is due to a susceptibility mechanism which has not been altered by age or opportunity for repeated exposure to pathogens, is rapidly succeeded by extreme susceptibility after the age of 6 months.

During this age period (6 months to 2 years), the infant first manifests susceptibility to measles, diphtheria, scarlet fever, and to many other infections, to some of which his vulnerability is extreme. At this time exanthema subitum preponderantly occurs and those who escape it are hardly ever demonstrably affected later in life. A considerable proportion of infants do have this disease, and it may be that nearly all have it although many cases are undetected. On the other hand, after this age of greatest susceptibility is past, resistance may develop by contact with the infectious agent without clinical illness being evident, or may result from a slow development of constitutional or racial resistance.

2. Case-to-case contact as a cause of this disease is extremely rare. To be sure, some three epidemics[4, 5, 6] have been described, but these are so at variance with the usual conditions under which the pediatrician sees this disease as to suggest strongly that they may not have been due to the same infectious agent. Known contact of a healthy to an infected infant rarely will result in disease and the infant so exposed may proceed to develop the infection at a still later time. One of twins may have the disease and the other twin escape. No mechanism for the spread of an infectious agent from one who is ill, such as applied to other of the common viral exanthemas would seem here to be responsible.

3. Exanthema subitum frequently occurs among infants who are most carefully protected against exposure to sick children or adults. It is unlikely that the etiological agent accounts for this disease in infancy and for an en-

tirely different syndrome in older children and adults. If the infectious agent is acquired from other human beings, which it seems reasonable to suppose, the source is probably a healthy person.

4. Exanthema subitum is often the very first febrile illness of the child, but, with a frequency which is perhaps significant, the infant will have had a minor illness, upper respiratory infection, digestive upset, or immunization procedure ten to fourteen days previously. This might suggest that these antecedent disturbances may further reduce resistance against an agent which was coincidentally present.

Consideration of an etiology which suits these conditions suggests several possible agents:

1. First exposure to one or several of the common bacterial pathogens might conceivably provoke this syndrome under the especial conditions of infantile immunity, and the eruption that occurs might be of an allergic nature. Our own study of throat and blood cultures, from which sources positive isolation of an infectious agent would be most likely to be successful, has given us no significant information. Other observers have obtained the same negative results. Blood cultures are sterile and the throat cultures show no constancy of flora and the absence of the common pathogens. Furthermore, if the infection were due to a common bacterial cause of disease, transmission by case-to-case contact would be expected more often.

2. It is imaginable that some fossil infection might be responsible, one which had been a cause of epidemic disease centuries ago and to which constitutional immunity is present in adults. Among these adults the agent frequently could be present as a latent infection and susceptibility to the pathogen might exist only in the immunologically immature. The idea has been developed by Dr. K. F. Meyer[7] that canine distemper, which is common among domestic animals, may represent an infection once prevalent among human beings to which racial immunity has been developed to a point where the infection has burned itself out in the human race and survives only in animals which later have been brought into the human environment. Against this attractive possibility for the explanation of the etiology of exanthema subitum is the fact that ordinary exposure does not result in disease with any frequency, even in individuals of the susceptible age group.

3. By comparison with the clinical course of other viral exanthemas, the etiologic agent commonly is thought to be a virus. This seems logical, although the exact method of transmittal does not yield to any direct analogy with these infections. We have considered the hypothesis that some virus was responsible which was most ubiquitous in healthy adults and older children, and probably occurred in their nose and throat secretions. Older persons might be immune as the result of past exposure or insusceptible on the basis of constitutional resistance. Some widely distributed virus to which exposure would be the rule might well be the cause of roseola under the peculiar conditions of infantile immunity.

Herpes simplex as an etiologic agent ideally suits this viral hypothesis. Widely distributed in healthy adults, it occasionally provokes evidence of infection under the provocation of some unrelated illness or injury. Immune bodies are present as a rule in adults and are absent in the age period during which exanthema subitum occurs. Herpes virus cannot unfailingly or easily be recovered from clinical material. It has not been possible readily to prove or disprove this virus as the cause of exanthema subitum.

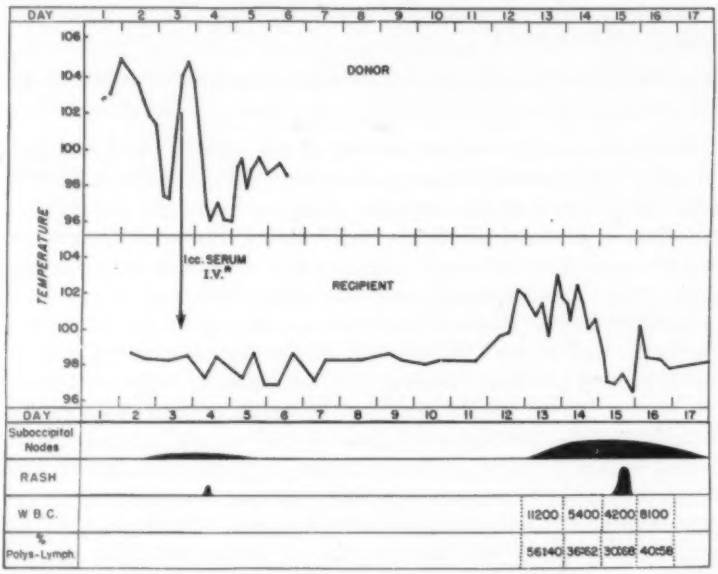

Fig. 1.—Direct transmission experiment. Serum taken from an 18-month-old infant in the pre-eruption stage of exanthema subitum and given to a suitable recipient produced the characteristic disease picture nine days later.

*I.V. = intravenously.

Our experimental studies started in an effort to isolate herpes virus or a herpes-like virus from throat washings. Breese[8] apparently had explored the same hypothesis but with a complete lack of success. From a number of patients which we have studied, herpes virus was obtained in a single instance from a throat washing taken at the height of the fever. It was possible in this patient to demonstrate the presence of serum-immune substances against herpes simplex virus on one occasion but we could not satisfactorily demonstrate its etiologic role. We have not attempted to produce the disease by inoculation of this virus. Following unsuccessful prolonged attempts to isolate the etiologic agent of exanthema subitum by utilizing rabbits, mice, ferrets, hamsters, and fertile eggs, we turned to a series of direct transmission experiments.

EXPERIMENTAL

1. *Direct Transmission Experiment.*—Blood was withdrawn from an 18-month-old donor on the third febrile day of an illness considered (and later

proved) to be exanthema subitum. Within five minutes thereafter, the blood cells were separated from the serum and under aseptic conditions 1 c.c. of the latter was injected intravenously into a 6-month-old susceptible recipient who had had no previous illness. The donor was isolated throughout the hospital stay and no other known or suspected instances of any communicable disease was present during the course of this experiment. The serum simultaneously was shown to be bacteria-free by suitable bacteriologic examination. Nine days after the injection, the recipient developed typical exanthema subitum

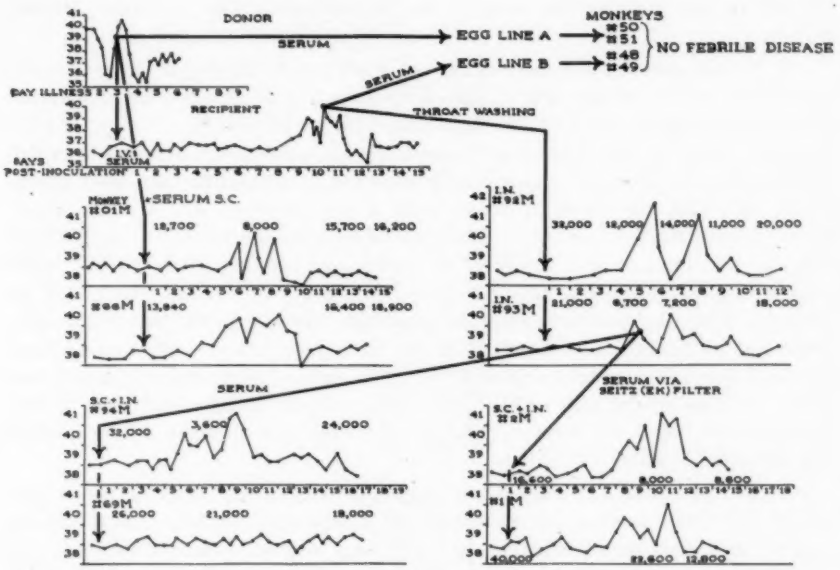

Fig. 2.—Studies in the transmission of exanthema subitum, demonstrating the production of a febrile response in monkeys through several passages after initial inoculation with human serum and throat washings.

I.V. = intravenously.
S.C. = subcutaneously.
I.N. = intranasally.
#—M = monkey number.

(Fig. 1). This consisted of three days of fever ending by crisis, early leucocytosis with subsequent marked leucopenia, enlargement of the suboccipital nodes on the second day of the disease, and a typical maculopapular rash which appeared almost immediately following the critical drop of temperature to characteristically subnormal levels. In contrast to the donor, who developed a fleeting rash which lasted for only about four hours, the recipient developed a rash which was very marked and persisted for approximately twelve hours.

2. *Transmission of Human Donor's Serum to Monkeys.*—The donor's serum utilized in the previous experiment was also inoculated subcutaneously (0.5 c.c.)

into monkeys No. 01M and No. 66M (Fig. 2).* Five days following this inoculation, monkey No. 01M developed a three-day febrile illness, characterized by a spiking temperature curve with a subsequent drop of the temperature to subnormal levels. It failed to develop adenopathy, exanthem or enanthem, but a drop in the white blood count did occur during the course of the disease. The other monkey (No. 66M), inoculated subcutaneously with the same material, became febrile on the fourth day and had a fairly sustained fever which persisted for five days with a subsequent drop of the temperature to subnormal levels. It also failed to develop any other symptoms. The animals used in this and subsequent experiments were 12- to 14-month-old rhesus monkeys, Macaca mulatta.

3. *Transmission of Recipient's Throat Washings to Monkeys.*—Throat washings taken on the second day of the recipient's febrile illness were inoculated by intranasal spray into two monkeys (No. 92M and No. 93M). Prior to injection the inoculum was treated with penicillin and streptomycin which was sufficient to render them bacteriologically inactive. On the fifth day after inoculation, No. 92M developed a fever, with a maximum of 42° C.—the entire febrile period lasting five days. During this time the white blood count, which initially had been 32,000, dropped to 11,000, but rose again to 20,000 on the twelfth day after inoculation. Monkey No. 93M, who similarly had been inoculated with the recipient's throat washings via the intranasal route, also developed a febrile illness on the fifth day after inoculation, with a subsequent maximal rise in temperature to 40.6° C. The entire febrile episode lasted four days. In this animal the white blood count, which initially had been 21,000, dropped to 6,700 at the onset of the fever but then rose to 18,000 on the twelfth day after inoculation.

4. *Transmission Experiments in Monkeys.*—Blood was taken on the second febrile day from monkey No. 93M, the serum separated from the cells, and the former then inoculated intranasally (0.5 c.c.) and subcutaneously (0.5 c.c.) into two monkeys No. 69M and No. 94M. One of the monkeys, No. 69M, failed to develop any febrile illness and the white blood count varied between 26,000 and 18,000. The other monkey, No. 94M, who received the same material by the same routes developed a fever on the fifth postinoculation day which lasted for five days, with a maximal temperature of 41.6° C. The white blood count fell from 32,000 to 3,600 on the seventh day after inoculation and subsequently rose to 24,000 on the fifteenth day after inoculation.

The same material (serum taken from monkey No. 93M on the second day of its febrile illness) was passed through Seitz EK filter and 0.5 c.c. each immediately inoculated, both subcutaneously and intranasally into two monkeys, No. 2M and No. 1M. Monkey No. 2M developed a febrile disease on the eighth day after inoculation, which lasted four days, with the maximum temperature being 41.6° C. The white blood count which was 16,000 at the time of inocula-

*In both of these monkeys, as well as in all subsequently reported, basal temperatures were obtained at a time when the animals were not exercised or excited. Temperatures were taken twice a day at the same hours for a period of between five and ten days prior to inoculation and no monkeys were used experimentally who showed spontaneous rise in temperature during this observation period. Cages were kept from direct exposure to sunlight and no climatic variations in temperature were of significance.

tion dropped to 8,000 on the second febrile day, and was 8,600 on the fifteenth day after inoculation. Monkey No. 1M had a febrile rise on the eighth day after inoculation, with the illness lasting four days, and the maximum temperature being 41° C. The white blood count, which was 40,000 initially, was 22,600 on the third day of the febrile illness and dropped further to 12,800 on the thirteenth day after inoculation.

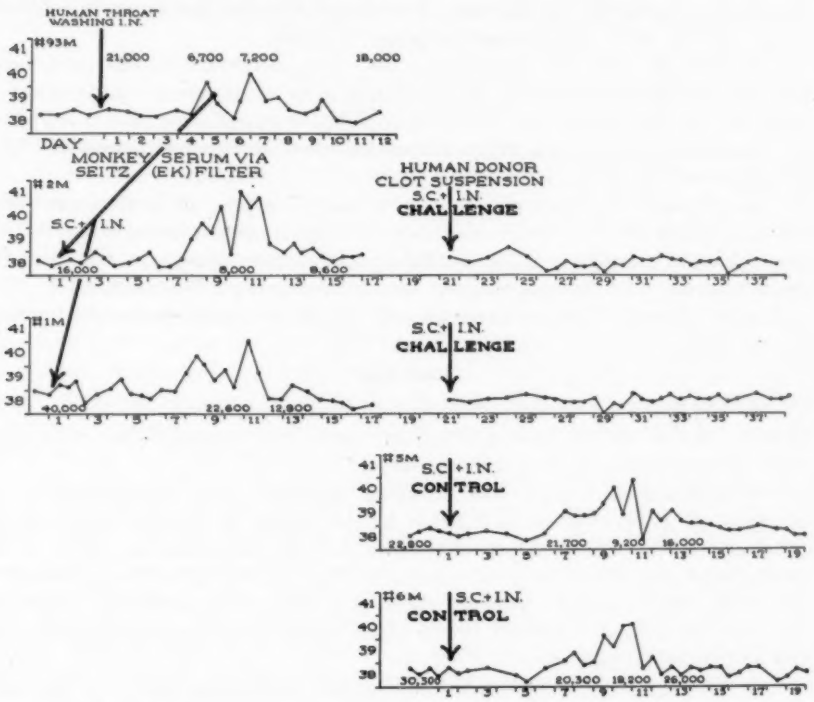

Fig. 3.—Challenge experiment utilizing convalescent monkeys.
S.C. = subcutaneously.
I.N. = intranasally.
#—M = monkey number.

5. *Challenging of Convalescent Monkeys With Human Donor's Serum.*—Monkey No. 2M which had previously developed a four-day febrile illness, following inoculation with monkey serum, was allowed to convalesce for nine days. Subsequently 0.5 c.c. of the original human donor's blood clot, suspended in saline, was inoculated both subcutaneously and intranasally. This monkey experienced no rise in temperature during the next twenty days. (Fig. 3.)

A second monkey (No. 1M) which also had a febrile illness following inoculation with monkey serum was challenged with this human blood clot inoculation by subcutaneous and intravenous injection. This monkey, too, failed to develop a fever in the following nineteen-day period.

At the same time that the challenge experiments were carried out, two control monkeys (No. 5M and No. 6M) received the identical clot suspension of the original human donor material by the same routes. Monkey No. 5M developed a febrile disease on the seventh day after inoculation with a maximum temperature of 40.9° C. and a total duration of illness of five days. The white blood count, which was 23,000 the day of inoculation, dropped to 9,200 on the fourth day of the febrile disease. Two days after the temperature returned to normal, the white blood count had risen to 16,000.

Monkey No. 6M was inoculated in the same manner with the same material and developed a similar febrile illness with a maximum temperature of 40.6° C. In this animal, the white blood count dropped from 30,500 to 18,200.

In this experiment the saline suspended blood clot that was used had been preserved at minus 45° C. for four months.

Acute phase human serum has been passed serially in fertile eggs without producing consistent lesions or death. Blind passage has been carried out through eight passages. Allantoic fluid pools of this passage, as well as of the third passage, have been inoculated into four monkeys, Nos. 50M, 51M, 48M, and 49M. None of these animals showed any febrile response during the next twenty days.

SUMMARY

1. The first experiment described has persuasively demonstrated the infectious nature of exanthema subitum, by means of a transmission experiment from a human donor to a susceptible subject.

2. Subsequent experiments utilizing monkeys have demonstrated the presence of a fever-producing agent in the serum of human beings on the third day of the febrile period of exanthema subitum illness, as well as in the throat washings of a susceptible recipient. It also was shown to be present in the serum of previously infected monkeys. This fever-producing agent has not been shown to be present in the blood of human patients during the first day of the febrile period.

3. The challenge experiments have shown that blood taken on the third day of the febrile period of exanthema subitum was still able to produce a febrile disease in control monkeys, but failed to do so in monkeys previously experiencing a febrile inoculation disease.

4. Egg passage material has, to date, failed to produce febrile reactions in four monkeys tested.

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CLINICAL DIAGNOSIS OF CONGENITAL HEART MURMURS BY MEANS OF THE SYMBALLOPHONE

A Double Stethoscope Making Use of Two Ears for Lateralization and Comparison of Sounds

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THERE are two classes of professional workers dealing with mammals, who deserve our respect and admiration. I refer to the pediatricians and the veterinarians. They deal with objective information largely, and such subjective information as they may obtain would appear to the unlearned, as I profess myself to be, as coming from unreliable sources. The child may express itself in language a mother or pediatrician may understand, but it is the grandmother who should be consulted. The veterinarian must get his leads from the rancher or pet owner who may report only that the animal will not eat, is bloated, cannot get up or make manure, or that the pig's tail has lost its curl. Although these revealing symptoms may be portents of prognostic significance, they are not diagnostic. The objective examination thus becomes the chief avenue to the solution of the clinical problem.

For some years I have been interested in devising ways to improve diagnostic techniques at the bedside on the assumption that physical diagnosis with history taking constitutes the foundation of clinical medicine. Any maneuver, device, or simple test which will permit us to use our special senses to better advantage will not only serve the interests of our patients better but will also stimulate the physician's intellectual growth and satisfaction. Any simple method which will permit us to make finer comparisons of physical signs will aid in the detection of the more obscure or minor deviations.

A few years ago, with the help of several colleagues, the symballophone was designed to make use of the natural functions of the two ears for the lateralization and comparison of sounds. In a number of reports,[1-9] we have discussed the basic principles involved and the practical use of this double stethoscope which transmits the sounds of each chest piece to both ears, but through differences in length and bore of the connecting tubes gives the impression that the sounds arise on one side or the other (Fig. 1). The device is of particular value to the pediatrician, because with it he may compare breath sounds over the two lungs during any respiratory cycle, however variable the respiratory rhythm may be or how difficult it may be to secure cooperation.

In the diagnosis of congenital heart lesions, the symballophone has become an instrument of extreme value. Average auditory acuity for detection of differences in phase or timing is a small fraction of a second (0.000030 second), based on the fact that sound travels in air at the rate of 332 meters

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per second or 1 centimeter in 0.000030 second, and the average normal human ear can detect this difference. Since the magnitude of differences in timing that we are called upon to detect are in the range of from 0.01 to 0.15 second, there should be no difficulty in doing so.

Fig. 1.—Symballophone as finally constructed after experimental and clinical studies. This diagram was first published in Kerr, Wm. J.: Stethoscope and Symballophone, Medical Physics, Otto Glasser, ed., Chicago, 1944, Year Book Publishers.

It is now demonstrated that audible murmurs do not travel in the blood stream as sound but travel with or on the pulse wave, in fact at a rate which is slightly slower than the pulse wave (10 to 15 meters per second), whereas if murmurs were propagated as audible sound, they would travel at the rate of more than 1,300 meters per second, or about 100 times the rate they can be demonstrated to travel. Murmurs produced at points in the blood stream, where congenital or acquired lesions interpose obstructions and cause faults in streamlining, travel in both directions but chiefly in the direction of the blood flow. Murmurs produced at some distance from the heart do not appear until the pulse wave reaches that point after the necessary delay conditioned on the pulse wave velocity. A point of departure for timing may be taken from the beginning of the first sound at the apex of the left ventricle or the apex beat by palpation.

If we consider first lesions of the aortic or pulmonic valve, it will be easier to comprehend the other lesions which are more often congenital in nature.

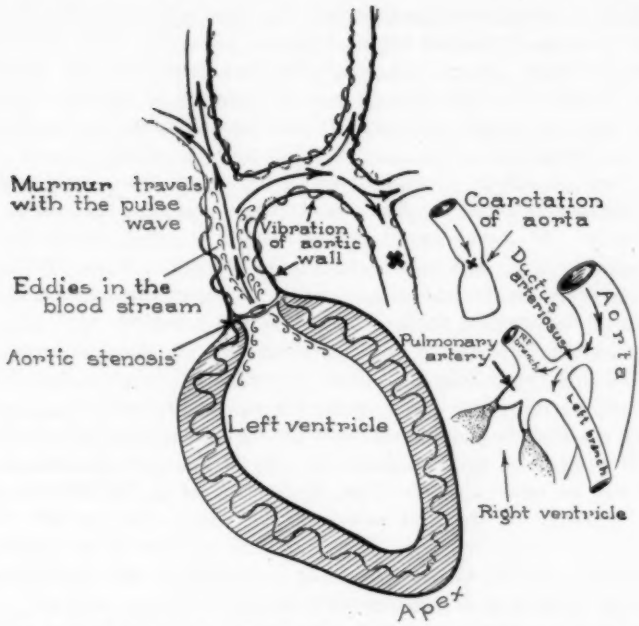

Fig. 2.—Diagram showing the course of the blood stream and the site of origin of murmurs in relation to lesions in the four sites of great importance in diagnosis. The timing of the murmurs is readily determined by use of the symballophone. This diagram was first published in Kerr, Wm. J.: The Symballophone: A Double Stethoscope for the Comparison and Lateralization of Sounds, Essays in Biology, in honor of Dr. Herbert M. Evans, University of California Press, 1943, p. 259.

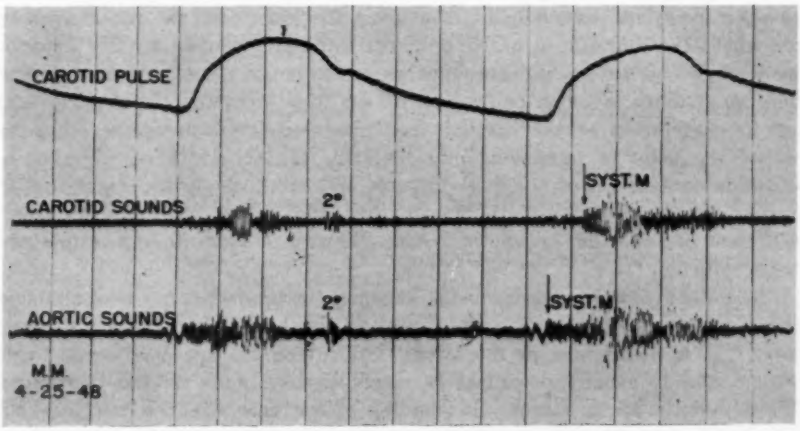

Fig. 3.—Simultaneous carotid pulse wave and phonocardiograms of sounds at carotid and arotic areas, showing the delay in time of arrival of the murmur of aortic stenosis at the carotid area. Timer registers at 0.10 second. This diagram was first published in Kerr, Wm. J., Harp, V. C., Rapaport, E., and Bierman, H. R.: Propagation of Murmurs and the Local Production of Vascular Murmurs in Relation to the Pulse Waves, Tr. A. Am. Physicians **61**: 308, 1948.

We have demonstrated graphically that the systolic murmur of aortic stenosis or pulmonary stenosis begins with systole of the ventricles. In aortic stenosis the systolic murmur is generally best heard in the second right interspace adjacent to the sternum and is propagated more or less widely along the major systemic arteries. If one listens with the symballophone, applying one chest piece over the apex of the left ventricle and the other over the point of origin of the systolic murmur at the second right interspace, it will be noted that the first sound at the apex and the murmur appear simultaneously. At more distant points along the great vessels the systolic murmur appears later and later, and at the carotid arteries the murmur is approximately 0.04 second later than the appearance of the first sound (Fig. 2). The timing of the systolic thrill over the carotid coincides with the murmur, and by palpating the carotid and the apex impulse simultaneously, it may also be noted that the systolic thrill over the carotid is delayed (Fig. 3).

The same comparisons can be made for pulmonary stenosis. In this case the systolic murmur is propagated through the pulmonary artery, but at the second left intercostal space adjacent to the sternum where the murmur is loudest it will be noted that the time of appearance of the murmur coincides with the beginning of the first sound at the apex. The systolic thrill also coincides with the apex impulse. If the systolic murmur is propagated widely over the chest, the time of appearance at points more and more remote from the pulmonic valve area is progressively later.

Let us now consider coarctation of the aorta and patent ductus arteriosus. In coarctation of the aorta there may be a murmur at the aortic area, but if there is a murmur over the usual location at the base of the neck between the left scapula and upper thoracic spine, it will be found to arise approximately 0.08 second after the beginning of the first sound at the apex. By placing one chest piece of the symballophone over the apex and the other over the area where the murmur is heard best, the difference can be readily detected. The combined palpatory and auscultatory technique is not so satisfactory since the sense of touch is not so delicate as the auditory comparison test. The murmur in coarctation of the aorta is not produced until the pulse wave has reached the point of narrowing; this explains the time interval elapsing between the contraction of the left ventricle and the time of appearance of the murmur in the upper left thorax at the usual site. Murmurs in cirsoid aneurysms and in other collateral vessels likewise show a late appearance time for the murmur.

In patent ductus arteriosus the murmur is produced in the pulmonary artery where the fistula from the arch of the aorta enters the pulmonary artery. It is heard best in the second left intercostal space adjacent to the sternum and is usually described as machinerylike, more or less continuous, with a systolic accentuation. In fistulas of extreme size the murmur may be insignificant. The timing of the accentuated phase is of the greatest significance in establishing the diagnosis. If one applies one chest piece at the apex to listen to the first sound and the other over the area where the murmur is of maximum intensity, it will be noted that there is a relatively long interval

between the time of appearance of the first sound and the murmur. This difference is approximately 0.12 to 0.15 second, which is readily detectable.

In some cases where a murmur is of extreme intensity and tends to obscure or damp out the other, it may be necessary to lift one side of the chest piece to equalize somewhat the intensities of sounds coming from two points.

Other congenital lesions will not be discussed in detail. Where multiple lesions are encountered, which is frequently the case, a differentiation is facilitated by this technique and a knowledge of the patterns of blood flow in the several anatomical anomalies.

Some skill can be attained by practice with the symballophone, but the exercise of the natural functions with which we are endowed permits a child of 2 years of age to detect, differentiate, lateralize, and compare sounds as well or better than physicians can, since some of us have suffered from diseases of the auditory apparatus or have lost tone perception with age. To understand and to use the symballophone requires study of the structure and dynamics of the circulation, which some physicians are loathe to pursue.

The stethoscope has become the symbol of the physicians, but it is unfortunate that more do not learn how to use it.

SUMMARY

The technique for the use of the symballophone in the differentiation of four of the common cardiovascular lesions has been described. These methods are of particular value in the study of congenital cardiovascular lesions.

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MULTIPLE CONGENITAL DISLOCATIONS ASSOCIATED WITH CHARACTERISTIC FACIAL ABNORMALITY

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WE HAVE recently encountered a series of six cases of multiple congenital deformities in young children, which follow a consistent pattern not previously recognized. Although the association of these several deformities in a patient may not have been well recognized, the individual deformities to be described are well known. These deformities involve primarily the major joints of the lower and upper extremities, the feet and hands, and the face. The most obvious and the most disabling deformity is that of bilateral anterior dislocations of the tibiae on the femora. This syndrome is further characterized by bilateral antenatal dislocations of the hip, bilateral equinovarus or equinovalgus deformities of the feet, and bilateral dislocation of the elbows.

All six patients have characteristic shaping of the hands and similar long, cylindrical-shaped fingers, which do not taper normally from base to finger tips. In contrast, the metacarpals are relatively short. The thumbs are usually spatulate. The facial configuration is most striking. The eyes are wide spaced, the forehead is prominent, and the nasal bridge is depressed, producing a flattened facies.

Associated findings in these cases include deformities of the soft palate, a cleft palate, a cleft uvula, and a midline groove in the uvula. Two cases present abnormal segmentation of the vertebrae, cervical and thoracic.

The temporomandibular, shoulder, wrist, and finger joints have not been involved by dislocations in any of our cases. Dentition has appeared and developed normally. Bone development has been normal except for molding, due to changes resulting from dislocation. Irregularity and asymmetry of some of the epiphyses and adjacent epiphyseal cartilages have been secondary to trauma and to the effects of the dislocation.

Mental development has been normal. The general physical examination has revealed no abnormalities in other systems with one exception, that of D. D., who had a mitral systolic murmur, thought to be functional.

Biopsy and autopsy material have not revealed any evidence of muscular abnormality, as is seen in cases of arthrogryposis multiplex congenita, or other muscular dystrophies or atrophies. Laboratory studies have not shown changes from the normal.

All of the siblings of these patients have been normal. The family histories have revealed no similar involvement.

Many references are made in the literature to varying types and combinations of congenital dislocations and congenital deformities. The occurrence of

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dislocations of the hips and knees, associated with deformities of the feet, has been reported by Chandler,[1] Kohler,[3] McFarland,[5] Sorrel and LeGrand-Lambling[6] and others. Congenital anterior dislocations of the knee are infrequent, but congenital dislocations of the elbow occur even less frequently. Kopits[4] found eleven cases of congenital knee luxations among 2,323 congenital deformities, which also included 923 hip luxations. Only isolated reference to cases of bilateral congenital dislocations of the hips and knees with associated bilateral congenital dislocations of the elbow can be found. Kaijser[2] records the only complete description of a case presenting bilateral dislocations of the knees, hips, and elbows, foot deformities, facial and hand abnormalities we could find.

The occurrence of six cases in a short time in one locality appears to be more than coincidental. It is our belief that many of the patients who present so-called tetralogic dislocations and deformities of the feet will also exhibit the facial, elbow, and hand abnormalities described above. Many case histories or reports do not clearly describe the deformities and merely state that the "skull was abnormal," or "the elbows are slightly stiff," etc.

Since we have found no characteristic biopsy, necropsy, or laboratory changes, we are not able to classify these cases pathologically or group them with any recognized entity.

Treatment has been chiefly directed toward securing stable knee joints for weight bearing. The foot deformities have been treated both surgically and by wedging plaster casts. We have not surgically attacked the hips. Hip dislocations have not given severe lordosis and we have preferred, so far, not to do radical hip procedures, since these children are doing so well functionally. Elbow function is excellent, although there is varying limitation of extension. We have done open reductions on the knees bilaterally, as detailed in some of the case histories, holding the position by capsular repair and plaster fixation, aided in two cases by a transfixation wire at the time of surgery.

The most striking visible clinical findings are the typical moon-shaped or flattened facies, anterior dislocations of the tibiae on the femora, and foot deformities. These cases have slight individual variations: one has normal elbows, one has insufficient acetabula without frank dislocation, two have had associated spine abnormalities, and three associated palate defects.

The following six cases represent our experience with this syndrome.

CASE 1.—M. C. This child was first seen at the Shriner's Hospital at the age of 5 months. She had been the product of a normal, full-term delivery of healthy parents on June 28, 1944. There were three siblings aged 13, 11, and 2 years, with no family history of neurologic or orthopedic abnormalities. Her first tooth erupted at the age of 10 months and the ensuing dentition was normal. The anterior fontanel was closed at the age of 14 months.

On examination she presented bilateral prenatal type hip dislocation, dislocation of both tibiae on the femora, and equinovarus of the right foot and an equinovalgus of the left foot. The elbows were not dislocated and the shoulders and wrists were normal. The hands and digits had the characteristic configuration. She presented typical facies with wide, prominent forehead, wide-spaced eyes, and depressed nasal bridge. There was no cleft palate present.

Her mental development was slightly below average for her age but not to an abnormal degree.

During her hospitalization, two unsuccessful attempts were made at closed reduction of the hips in late 1945. The knees were corrected by surgical intervention in January, 1946. At the time of knee reduction, muscle biopsies were taken, which were reported to be entirely normal. At the time of surgery, characteristic changes were found in both knee joints. The dislocated position

Fig. 1.—L. L. L. and M. C. Note characteristic prominent forehead, depressed nasal bridge, wide-spaced eyes, and flattened facies.

of the femora had allowed molding of the tibiae so that the normal tibial plateau was slanted posteriorly 45 degrees. The anterior cruciate ligaments were markedly elongated. The infrapatellar tendons were found contracted and were necessarily lengthened by including a cuff of tibial periosteum at the time of reduction. Postoperatively, reduction was maintained by suturing the pes anserinus and biceps anteriorly after appropriate shortening of these structures. A plaster cast was placed to maintain the reduction.

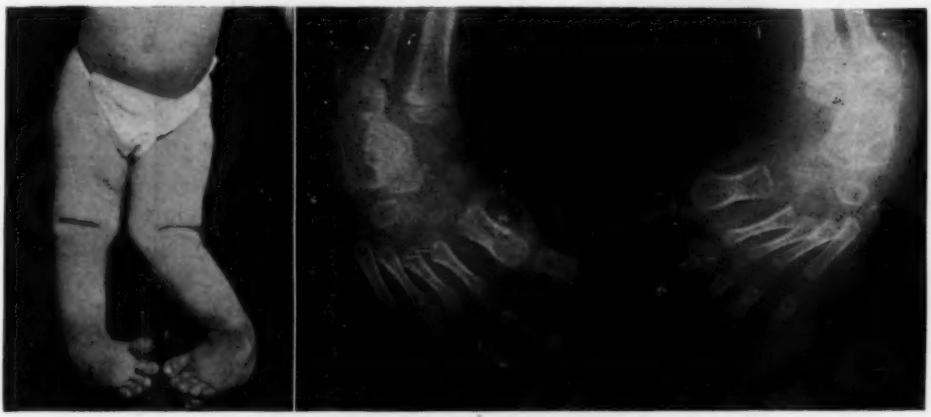

Fig. 2.—D. D. Note bilateral talipes equinovarus and skin crease at knee, indicating anterior dislocation.

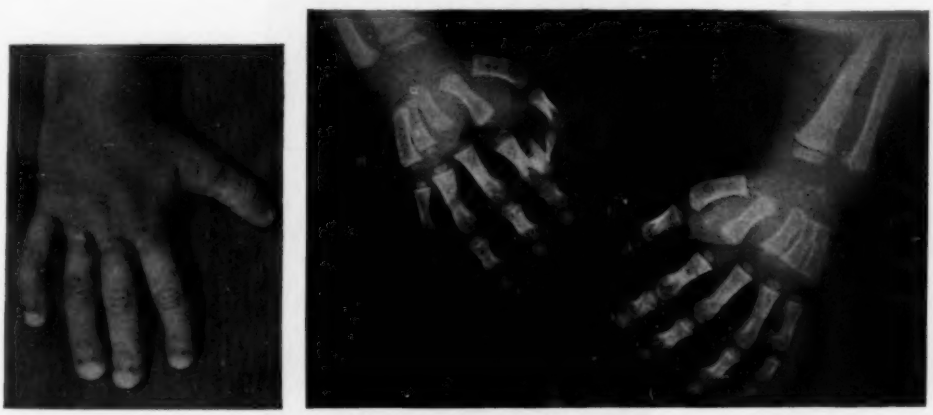

Fig. 3.—Characteristic cylindrical fingers and short metacarpals.

When the patient was last seen by us, Nov. 23, 1949, the right long leg brace had been discarded and this leg was stable without support. The left knee, however, was still somewhat unstable and the long leg brace was continued. At this time, the left knee flexed to 90 degrees and extended to 180 degrees. The right knee flexed to 60 degrees and extended to 180 degrees.

CASE 2.—D. D. This male child was first seen by us at Shriner's Hospital at the age of 2½ years. He was born at term June 30, 1944, following a normal pregnancy, with no abnormality of position noted. There were two siblings 10 and 4 years older than the patient, and both were normal. There was no family history of neurologic or orthopedic abnormalities. The general development of this patient was usual for his age.

A.

B.

Fig. 4.—*A*, M. C.: note bilateral hip and knee dislocations. *B*, D. D.: bilateral dislocations of elbows.

The child was never a feeding problem. He sat at the age of 6 months, stood at 12 months, and spoke words at 12 months. His general mental development has continued to be normal. When first seen by us, his fontanels were closed. A right inguinal hernial repair had been done. His family stated that he had had a left otitis media with onset at the age of 2 months. It was noted that his head circumference was 52 cm., which was beyond the ninetieth percentile for his age, and chest measurement was 46 cm., which was below the tenth percentile for this age.

On examination, he presented bilateral dislocations of the hips, knees, and elbows, with bilateral talipes equinovarus. The thumbs were abnormally wide, almost double their normal width, and spatular in shape. The other fingers on either hand were cylindrical. The face was typical, with prominent forehead, wide-spaced eyes, and depressed nasal bridge.

He was admitted to Shriner's Hospital in February, 1947, where no attempt was made to correct either hip. His feet were corrected by wedging plasters, followed by plantar dissection and os calcis skeletal traction. Both knees were surgically reduced in March, 1947, after the technique used in the case of M. C., and with similar pathologic findings at the time of surgery. Postoperatively, the knees were held in position with plaster fixation, and upon removal of the plaster, he was fitted with long leg braces.

When the patient was last examined by us, he had discarded both long leg braces. His knees have remained corrected, though the feet present some residual deformity. The range of knee motion is good but not normal.

CASE 3.—G. M. This child was first seen at the University of California Hospital. He was born at term Jan. 14, 1947, following a normal delivery of normal parents. There was no familial history of similar abnormality. There was one male sibling 13 years his senior. His head and feet presented together at the time of delivery, so that his legs must have been completely flexed on his body, as in the case of E. B. His birth weight was 6 pounds, 10 ounces. During the first 10 months of life he was treated by home manipulative procedures.

On admission to the hospital at this age, his psychometric rating gave him an I.Q. of 101. It was noted that the dentition was normal. At 10 months, the anterior fontanel was almost closed. Laboratory work, including serum calcium, serum phosphorus, and serum phosphatase, was normal.

On clinical examination, it was noted that he presented bilateral dislocation of elbows and knees, as well as bilateral equinovarus. The hips were questionable. By x-ray the femoral heads appeared to be normally placed but the acetabula were very shallow and steep. The facial contour was similar to the others of this group. There was a midline groove in the uvula. The fingers were disproportionately long and cylindrical.

On Dec. 15, 1947, his right knee was successfully operated upon. On Jan. 14, 1948, the left knee was similarly operated upon and the child died that evening of what was thought to be, clinically, a respiratory anesthetic complication. At surgery, the tibial plateaus were found to be normal. The anterior cruciates were greatly elongated, with no sign of the posterior cruciate. There was, however, marked flattening of the anterior femoral condylar surfaces, due to tibial pressure.

A complete autopsy was performed on the following day with appropriate material taken for examination, according to the usual custom. No gross or microscopic abnormalities, other than clinically noted above, were found. A special note should be made that the striate muscle was normal. A complete examination of the brain was done by the neuropathologist and no abnormalities were noted.

CASE 4.—E. B. This child was first seen at Shriner's Hospital in February, 1944, but was transferred to the University of California Hospital and then finally to Children's Hospital in San Francisco. She was born at term on April 30, 1943, following a normal pregnancy. At delivery, the legs lay alongside the body, so that the feet and head presented together. Her sister, 6½ years her senior, is entirely normal in every way, and there is no history of familial neurological or musculoskeletal difficulties.

For the first three months she slept in the fetal position, with legs alongside her body and head, but gradually her sleeping position became more normal except for her fixed dislocations.

Passive manipulative therapy was begun in May, 1944, and she was finally admitted to the University of California Hospital in August, 1944. The records at that time state that she had bilateral dislocation of the knees, bilateral equinovalgus deformity of the feet, bilateral elbow dislocations, and a cleft uvula. Bilaterally, the thumbs and large toes were small. The other fingers were characteristic in their cylindrical rather than tapering appearance. The facies also were typical, with the appearance of a decreased anterior posterior diameter, wide-spaced eyes, flattened nasal bridge, and flattened face. Both dentition and fontanel closure were normal. Her mental development was normal and there were no deformities other than the musculoskeletal system.

During numerous entries until 1948, this child was hospitalized approximately eight months at the University of California, where unsuccessful attempts were made to reduce hips and knees, and also to correct the feet.

From 1948 to 1950, while at Children's Hospital, closed reductions were unsuccessful. Recently, however, the left knee was treated by open reduction, although it is, as yet, too early to state the final outcome. It is also of interest to note that both fibular heads remain dislocated at the tibiofibular proximal articulation.

CASE 5.—L. L. L. This child was first seen at Shriner's Hospital where her mother gave the history that she was a breech delivery on April 17, 1948. At the time of her birth her mother was 22 years of age and her father 20 years of age. Pregnancy had been normal except that it was terminated by premature delivery during the seventh month. There was no history of other disease or deformity in this family. There is one younger normal sister.

The child has had a normal mental development and is well adjusted to her environment. She has seemed particularly susceptible to upper respiratory infection and has had recurrent kidney infection. When first seen by us, both hips had been reduced, but the reduction seemed inadequate in that the femoral heads stood abnormally far from the insufficient acetabula. There was a bilateral anterior dislocation of the tibiae on femora, bilateral equinovalgus deformity of both feet, as well as bilateral dislocation of both elbows. An incomplete cleft palate was present. The head was characteristic in shape with its flattened anteroposterior appearance, wide-spread eyes, and depressed nasal bridge. By x-ray, there was a congenital failure of segmentation in the upper thoracic region. The fingers were of the usual cylindrical type. However, dentition and fontanel closure were normal.

At this time, open reductions have been performed on both knees, but they have been so recently done that we have no way of knowing the final result.

CASE 6.—B. G. This child was born in San Francisco Hospital on Nov. 24, 1947. The birth weight was 10 pounds, 14 ounces. There is no family history of neurological or orthopedic abnormality. There are seven older children in this family, all normal.

On initial examination, it was noted that the child presented bilateral dislocations of both hips, knees, elbows, and equinovarus of both feet. On Nov. 23, 1948, at the age of 1 year, a note in the record stated that the anterior fontanel was closed. Also, x-ray revealed a spina bifida in the cervical spine. Her dentition was normal. The shoulders were apparently normal, as were hands and wrists, although the fingers were of the cylindrical type. The aforenoted characteristic facies with prominent forehead, wide-spaced eyes, and depressed nasal bridge were readily recognized. She did not present a cleft palate. Blood cholesterol and blood iodine studies were well within normal limits. A muscle biopsy was done, which was reported normal.

On March 8, 1949, the right knee was reduced by open reduction, and on Dec. 16, 1949, a similar reduction was carried out on the left knee. A Kirschner wire fixation was used across the femur and into the tibia in each knee. During the procedure, the semilunar cartilages were removed, as well as both anterior and posterior cruciate ligaments.

This child is at present walking without support, although the knees are slightly unstable.

SUMMARY

Six cases of multiple congenital dislocation have been separated as an entity from the confusion of congenital anomaly. They are characterized by flattened facies, with prominent forehead, depressed nasal bridge, and wide-spaced eyes; bilateral dislocations of the elbows, hips, and knees; equinovalgus or equinovarus of the feet; cylindrical fingers that do not taper normally; occasional cleft palate, or other palate abnormalities; and occasional associated failure of spinal segmentation.

We wish to express our appreciation to Dr. Francis Cox for allowing us to include the case B. G. from the Stanford Service of San Francisco City and County Hospital.

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HEMOLYTIC DISEASE OF THE NEWBORN INFANT (ERYTHROBLASTOSIS FETALIS)

A Study of the Pathologic Lesions of Twenty Cases

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SINCE the observation that hemolytic disease of the newborn infant is the result of incompatability of the mother's and infant's blood, most of the published reports on this disease have been concerned with its serologic aspects. Comparatively few reports on the equally fascinating anatomic and histologic alterations seen in this disease have been presented.

The literature on hemolytic disease of the newborn (erythroblastosis fetalis) stresses the morbid anatomy of the blood-forming organs.[1, 2] It is apparent, however, that there is injury to cells other than erythrocytes, and that hemolysis and excessive hemopoietic regeneration are only a part of the total disease process. Lesions in many tissues have been commented upon only briefly and therefore deserve further study.

The purpose of this report is to describe and illustrate the pathologic lesions in a group of twenty newborn infants with several forms of hemolytic disease.*

GROSS OBSERVATIONS

Of the twenty infants, six were stillborn, five lived nineteen hours or less, eight lived three days, and one died at nine days of age. Three of the six stillborn infants showed cutaneous desquamation and maceration.

Four infants showed no external evidence of icterus or edema and died of causes other than erythroblastosis. Two were stillborn, having died of intrauterine asphyxia during labor, one from prolapse of the cord, and one presumably from polyhydramnios. Two other infants died two and seven hours after birth, respectively, one from pulmonary atelectasis and one from a congenital defect of the diaphragm. Another stillborn macerated infant showed neither icterus nor edema.

Fifteen of the infants had icterus or edema or both. Four showed edema alone. Of these, two were stillborn, one lived only one hour and one lived nineteen hours. Eleven were icteric; eight of these died on the third day, one died on the ninth day with exfoliative dermatitis and progressive anemia, one died at fourteen hours, and one was stillborn.

From the Division of Pathology, University of California School of Medicine, San Francisco, and the Mills Memorial Hospital, San Mateo.

*This group of twenty infants was selected for further study from a larger group of infants dying of hemolytic disease, because complete blood grouping had been done on the infant, mother, father, and in many instances on the siblings as well. The mothers of sixteen Rh-positive infants were Rh negative, and significant titers of Rh antibodies were demonstrable in the serums of each mother. Three infants were siblings and were Hr′ positive. Their mother was Hr′ negative, and in each pregnancy had an increasing anti-Hr′ titer of her serum. The mother of one infant was Rh negative, but anti-Rh antibodies were not demonstrable although both the infant and father were Rh positive. In this instance, the mother was group O while the father, infant, and several siblings were group A. Post partum, the mother developed an anti-A titer of 1:65,000 without significant elevation of her anti-B titer.

There were three sets of twins. Two sets were identical and one set was fraternal. Four of these infants died at three days of age with icterus and kernicterus, and had identical appearances and clinical courses. Two twin siblings showed differences in size, weight, and degree of edema at birth (Fig. 1). The edematous infant lived one hour and the nonedematous, slightly icteric, infant lived fourteen hours after birth.

Fig. 1.—Twin infants, one showing edema and the other mild icterus.

The obviously edematous infants were not icteric. Their edema was most pronounced in the head and face. The icteric infants with two exceptions showed some edema, usually localized to the dorsal surfaces of the hands and feet and to the external genitalia. Only one icteric infant showed facial edema. Edema of the anterior thoracic and abdominal walls and the presence of bile-stained ascitic fluid were demonstrable in the majority.

The range of body length in this group of infants was 32 to 52 cm. The range of body weight was 610 to 4,820 grams. The body weights of the four infants showing only edema were significantly greater than the weight range of normal infants of the same body length. Four other infants were overweight for their length; of these, two had both edema and icterus, one was icteric and had exfoliative dermatitis, and one stillborn showed no external evidence of disease.

The weight of the hearts of eleven of the infants exceeded the average cardiac weight of normal infants of the same length.[2] The range of increase

in weight was from 1 to 21 grams (average 9 grams). Those infants showing the greatest increase in heart weight were those with significant degrees of edema. Three of the heaviest hearts were from stillborn infants. There were no structural abnormalities noted. The chambers were generally dilated. A few hearts had small epicardial asphyxial hemorrhages. The endocardium, the aortic intima, and the adventitia of the great vessels in the infants with severe degrees of icterus were bile stained.

The thymus glands of four infants weighed from 3 to 10 grams more than the average normal thymic weight. Three of these glands were from infants showing neither icterus nor edema. In seven infants the glands weighed 1 to 4 grams less than the normal average weight. In most instances these glands appeared smaller than normal when viewed in situ. No other gross abnormalities, except for petechial hemorrhages in a few instances, were seen.

The thyroid glands of all infants in this group were of normal size and appearance.

Fig. 2.—Adrenal glands showing opaque chalky streaks and cortical layers.

The weight of the liver in twelve infants was increased from 15 to 240 grams above the normal average weight. Three livers were from two and one-half to three times the normal average weight. Of the four infants in this group without icterus or edema, the liver of only one was enlarged to twice the normal average weight. Of seven other livers, which were one and one-half to three times the normal average weight, six were from icteric infants and one was from an edematous infant.

The spleens of the majority of infants were enlarged from two to six times the normal average weight. Of the four infants without icterus or edema, three had spleens of normal weight and one had a spleen of twice normal weight. Of eleven spleens enlarged three times or more, eight were from icteric infants.

The pancreas was of normal size and gross appearance in all cases.

The adrenal glands of these infants showed consistent alterations. With three exceptions, the combined adrenal weight was greater than the average normal weight for the two glands. The increase in weight varied from 0.4 to

9 grams. The greatest increase in weight was four times the normal average. Of the three patients with glands which weighed less than the average normal, two were icteric and one showed neither icterus nor edema. The combined adrenal weights in these latter three infants were 1 to 4 grams below the average normal.

Fig. 3.

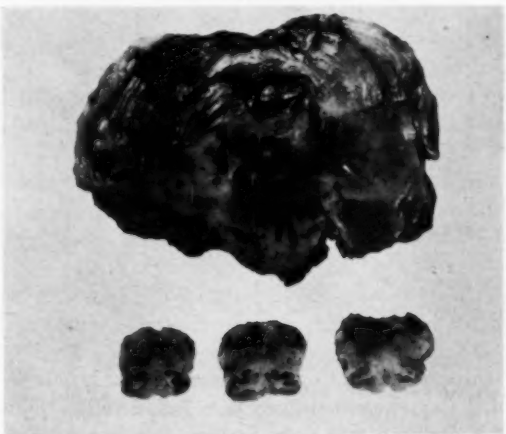


Fig. 4.

Fig. 3.—Medulla and cerebellum showing nuclear pigmentation.
Fig. 4.—Cerebrum showing intense diffuse pigmentation.

The cortical layers of the adrenal glands of all but two infants appeared thickened and generally had a grayish or yellow, translucent, succulent appearance (Fig. 2). The inner cortical layer was red, congested, and appeared mildly hemorrhagic in only a few glands. In glands with narrow cortices, small scattered areas of gray translucent tissue were visible in the cortical layers.

All adrenal glands in this group of infants showed yellow or white streaks in the inner cortical layer, extending in a radial direction toward the capsular

surface. These areas appeared opaque or chalky and were in distinct contrast to the adjacent glistening cortical tissue (Fig. 2).

The combined weight of the kidneys was greater than the average normal in 60 per cent of the infants. The increase in weight ranged from 4 to 13 grams with the edematous infants showing the greatest increase. The icteric infants showed diffuse bile staining of their renal parenchyma with few exceptions. Several had clumps of bright yellow amorphous debris in the calyces and pelves. The kidneys of two edematous infants were unusually pale. A renal vein was occluded by a thrombus in one infant.

There were numerous 0.5 mm. brown nodules surrounded by zones of congestion in the gastric mucosa of one icteric infant. Abnormalities of the gastroenteric tract were not observed in the other nineteen infants.

Icteric staining of the brain was observed in five of the eleven icteric infants, four of whom were twins. In the fifth (nontwin) infant, light yellow icterus was limited to the lentiform and caudate nuclei of the cerebrum, to the dentate nuclei of the cerebellum, to the inferior olivary nuclei and to the nuclei of the cranial nerves lying adjacent to the floor of the fourth ventricle (Fig. 3). Pale yellow pigmentation was limited to the basal nuclei of the cerebrums in one set of twins.

The brains of the second set of twins were intensely icteric. The first twin dying on the third day showed diffuse pale lemon-yellow pigmentation of the entire brain. This staining was more intense and had a brighter yellow color in the cerebral basal nuclei, the entire hippocampal gyri, cerebellar dentate nuclei, the medullary olivary nuclei and the medullary nuclei adjacent to the floor of the fourth ventricle. Yellow pigmentation of the gray matter of the spinal cord was also observed. The second twin who died sixteen hours after the first had even greater pigmentation of the brain (Fig. 4). There was a diffuse deep yellowish-tan color of most of the brain while certain localized portions were a deep orange. This was particularly distinct in the thalamus, internal capsule, and lentiform nucleus. The fornix, cerebellar vermis, and the medullary nuclei near the fourth ventricle were similarly though less deeply stained. The dentate and the olivary nuclei had the same yellowish-tan color seen throughout the brain but had no orange pigmentation. The corona radiata were bilaterally shrunken, had a gelatinous quality and also appeared deep orange. The gray matter of the spinal cord had yellowish-tan pigmentation.

MICROSCOPIC OBSERVATIONS

The microscopic sections of approximately sixty newborn infants without hemolytic disease served as control material. The ranges of age, body length, and period of survival after birth for the control group were the same as those of the erythroblastotic infants.

There were no significant microscopic alterations of the cardiac tissues despite the increased cardiac weight found in the majority of infants. Neither the myocardial nuclei nor fibers appeared hypertrophied. Vacuoles in the myocardial fibers, staining neither for fat nor glycogen, were present. These were not different from those seen in nonerythroblastotic infants.

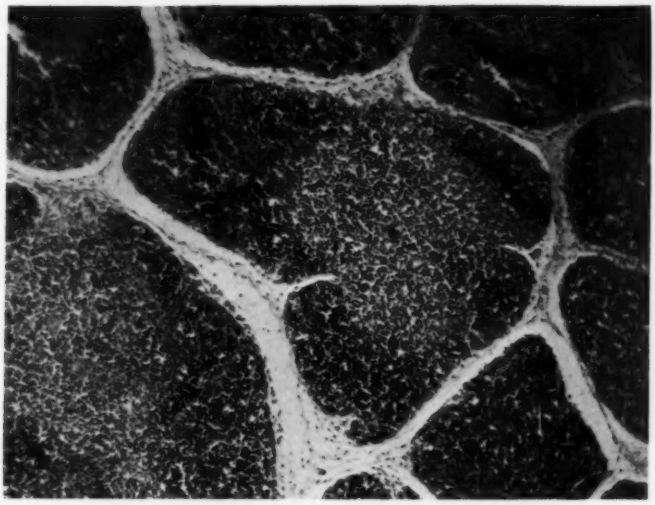


Fig. 5.—Thymus gland showing decrease in size of lobules. (Hematoxylin and eosin. ×80.)

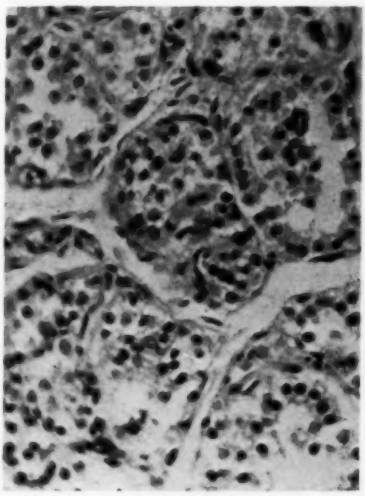


Fig. 6.

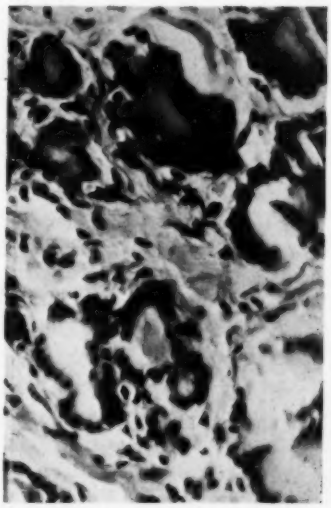


Fig. 7.

Fig. 6.—Hyperplasia of thyroid gland. (Hematoxylin and eosin. ×320.)
Fig. 7.—Interfollicular fibrosis of thyroid gland. (Hematoxylin and eosin. ×320.)

The thymus glands of 60 per cent of the infants had lobules which were smaller than those of normal glands (Fig. 5). This change was found in both hydropic and icteric infants but was twice as common in the latter group. It was observed in two infants without external manifestations of the disease. Although there appeared to be a proportionate decrease in the amount of both cortical and medullary tissue, the cortex was unusually thin and often consisted of a narrow band of lymphocytes. Peripheral lymphocytes were absent in some lobules. The medullary corpuscles contained calcific deposits. Edema of the interlobular septa was observed in a number of glands. Hemopoietic foci were seen both within the lobules and in the interlobular septa of only a few glands in this group.

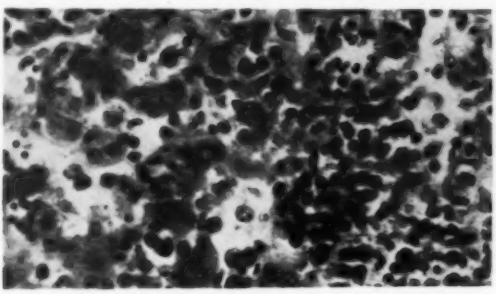


Fig. 8.—Liver showing excessive hemopoiesis. (Hematoxylin and eosin. ×320.)

All but one thyroid gland from this group of infants appeared hyperplastic as compared to the normal (Fig. 6). Generally, the follicles were smaller than normal and were formed by tall columnar cells. In almost all glands colloid was absent, and the follicular spaces were occupied by many desquamated epithelial cells. There was distinct interlobular and interfollicular fibrosis in two glands (Fig. 7).

The liver of each infant in this group was the site of abnormal hemopoiesis (Fig. 8). The degree of this process was not related to the severity of the icterus, since the hydropic stillborn infants showed as great a hemopoietic proliferation as the icteric ones. Three of the four infants without external manifestations of disease likewise had excessive hepatic hemopoiesis.

The hemopoietic foci, although diffusely distributed throughout the parenchyma, tended to lie in large groups which filled many sinusoids. While the majority of cells were early erythroblasts, with fewer more primitive erythroid cells and normoblasts, myeloid cells and occasional megakaryocytes with lobulated nuclei were also observed in the majority of livers. The erythropoietic cells in each group tended to be in the same stage of maturation.

The cords of hepatic parenchymal cells characteristically showed tremendous distortion and compression. It was apparent that the severity of this process paralleled the amount of hemopoietic tissue and, in the few livers with only mild hemopoiesis, the cell cords were not altered.

Distortion of the liver cords was accompanied by pronounced degenerative changes in the hepatic parenchymal cells. Outlines of cells were often indistinct and frayed. Coarse granulation and vacuolization of the cytoplasm was a prominent feature. The glycogen content of the cells was usually diminished.

In almost all livers in this group many of the hepatic cells were vacuolated. Not all the vacuoles stained with scarlet red. Fading or fragmentation of the nuclei of hepatic cells was seen in a few foci. In the most severely damaged livers groups of hepatic cells had disappeared, leaving a network of coarsened reticulum fibers (Fig. 9).

Generally both parenchymal and reticuloendothelial cells contained pigment granules. The amount of hepatic pigment did not appear to have any relationship to the presence or absence of icterus. Not all the pigment present stained with Prussian blue. In one liver the reticuloendothelial cells were greatly enlarged and vacuolated but contained minimal amounts of pigment.

The reticulum appeared normal in the livers with lesser degrees of hemopoiesis. In those livers with extreme hemopoiesis and hepatic cellular degeneration, the reticulum fibers were coarsened, frayed, and split. This alteration was greatest in areas where hepatic cells had disappeared.

The severely damaged livers also showed evidence of biliary obstruction. Masses of bile were commonly found in small bile ducts and in biliary canaliculi.

Hepatic cellular regeneration, characterized by moderate nuclear pleomorphism and hyperchromatism, was evident to a minimal degree. No distinct regenerating nodules were observed.

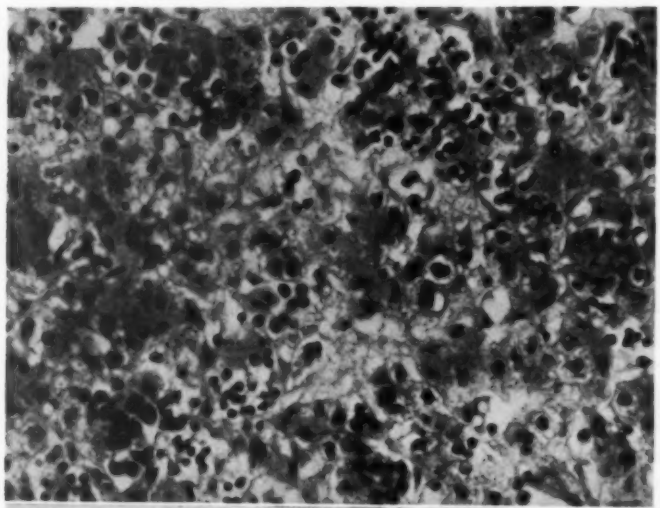
The spleens of most of these infants had an abnormal microscopic appearance. There were no differences between the spleens of the icteric and the hydropic infants. Generally the lymphoid follicles were extremely small. They were absent in several spleens and in one instance had been replaced by groups of hemopoietic cells. Spleens of two of the four infants without icterus or edema had normal lymphoid follicles. The sinusoids and intersinusoidal spaces were usually filled with blood. Diffuse hemopoiesis in the splenic pulp was present in all cases, and in one was also seen in the trabeculae. Splenic hemopoiesis was minimal in the four infants without external evidence of disease. Sinusoidal dilatation was not a prominent feature. One spleen with considerable diffuse hemopoiesis showed a distinct hyperplasia of reticuloendothelial cells throughout the pulp.

There was significant microscopic alteration of the pancreas of all infants. Although there were only one or two random pancreatic sections available for study, the pancreatic islets generally appeared more numerous than in the normal organ. Some pancreatic lobules consisted largely of islet tissue (Fig. 10). In most cases there was also a striking enlargement of the islets although, in one-third of the cases, they were of normal size or smaller. They generally were poorly defined and not demarcated sharply from the surrounding acinar tissue. Usually the islet cells were arranged in a disorderly fashion. In all cases there was some degree of cellular pleomorphism and nuclear hyperchromatism and, in the majority, these changes were extreme (Fig. 11).

The majority of pancreases had well-defined interlobular edema and fibrosis. In one, there was intralobular fibrosis associated with acinar atrophy and infiltration with eosinophilic leucocytes.

Small hemopoietic foci were usually seen in the lobules and interlobular septa. In one pancreas, hemopoietic tissue comprised large segments of lobules (Fig. 12).

Fig. 9.



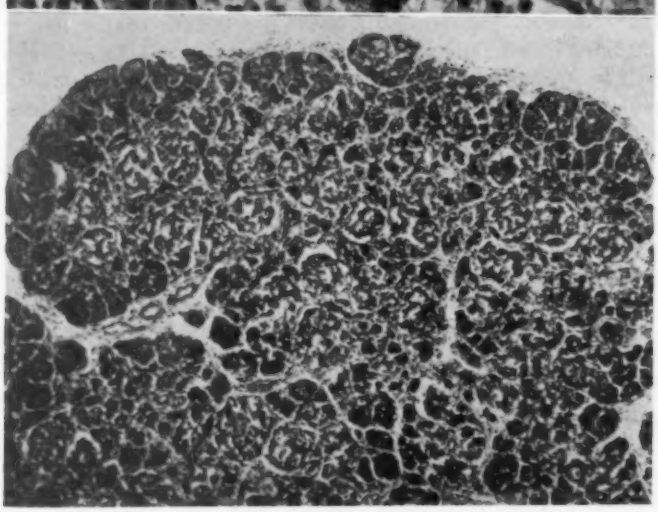


Fig. 10.

Fig. 9.—Liver showing loss of parenchymal cells with condensation of reticulum. (Hematoxylin and eosin. ×320.)

Fig. 10—Pancreatic lobule showing abundance of islet tissue. (Hematoxylin and eosin. ×80.)

All the adrenal glands in this group of infants had similar consistent microscopic lesions. These glands were distinctly different from those of normal newborn infants. The capsules of some glands were mildly thickened, and small collections of hemopoietic cells and macrophages containing pigment were occasionally observed.

Fig. 11.

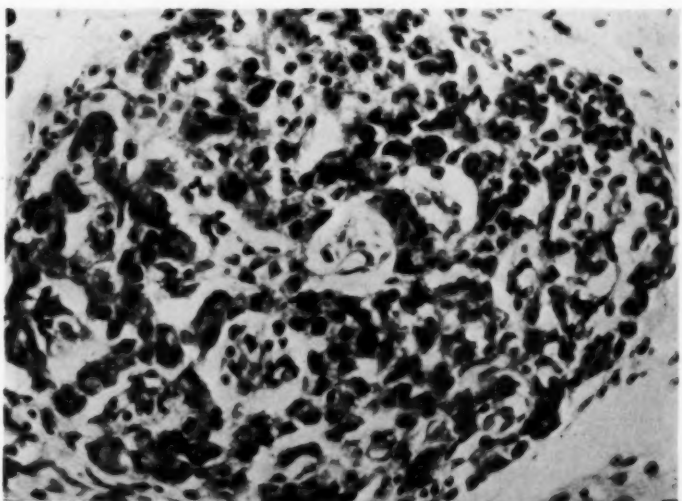


Fig. 12.

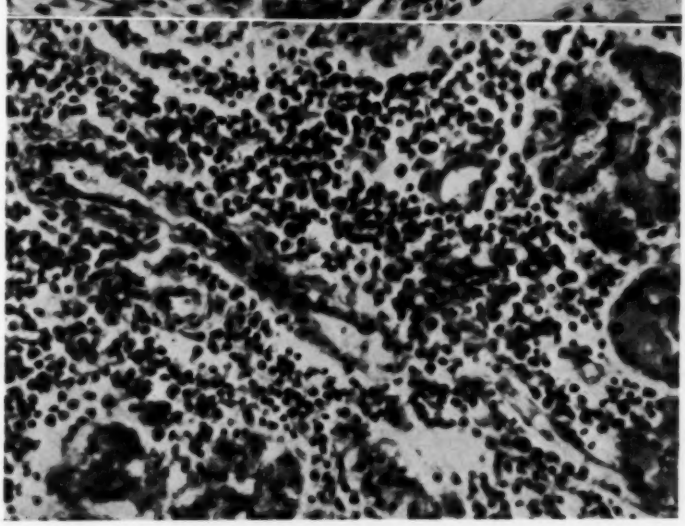


Fig. 11.—Pancreatic islet showing extreme nuclear pleomorphism and hyperchromatism. (Hematoxylin and eosin. ×320.)

Fig. 12.—Replacement of pancreatic acini by hemopoietic tissue. (Hematoxylin and eosin. ×320.)

These glands had a thin glomerular layer which was more clearly demarcated from the fascicular layer than is the case in normal glands. The epithelial cells of the glomerular layer were small, fairly uniform, and had small amounts of granular, nonvacuolated cytoplasm. The cells comprising the fascicular and outer reticular layers were considerably larger and had both larger nuclei and greater amounts of cytoplasm than those of the glomerular layer. The cells of the inner reticular layer closely resembled those of the glomerular layer in a few glands.

Fig. 13.—Adrenal cortex showing rows of vacuolated cells. (Hematoxylin and eosin. ×80.)

The majority of cells of the two inner layers showed pronounced vacuolization of their cytoplasm and had unusually distinct cellular borders. In many cells there were only a few fragments of eosinophilic granular material representing nonvacuolated residual cytoplasm. Fewer cells showed little or no vacuolization of their cytoplasm which was finely granular and eosinophilic. These latter cells were usually confined to the fascicular layer, where rows of these alternated with rows of vacuolated cells. These latter cellular columns of vacuolated cells, lying perpendicularly to the capsular surfaces, corresponded to the opaque chalky streaks which were visible on the sectioned surface of these glands (Fig. 13). Brown pigment granules were present in some cells.

A variety of degenerative and necrotic changes were observed in the epithelial cells of the two inner layers. Pyknotic shrinkage and fading or complete loss of nuclei were often present and were accompanied occasionally by fragmentation of the cytoplasm and loss of distinct cellular borders. There were focal zones of acute necrosis in a few glands. These small groups of acutely necrotic cells were surrounded by neutrophilic leucocytes.

Calcification of single necrotic cells, small groups of cells, or of larger necrotic segments of the cortex was found in glands of several infants (Figs. 14 and 15).

In general, the cortical layers were less vascular than those of normal glands. Vascular congestion of the inner cortical layers was generally focal in distribution and was present in a minority of glands. This congestion had little or no resemblance to the severe congestion associated with isolation and dissolution of cells of the innermost layer of the normal gland of the newborn infant. Small hemopoietic foci were observed in the glands of only about 25 per cent of the patients. There was an early mural thrombus in a large central adrenal vein in one patient.

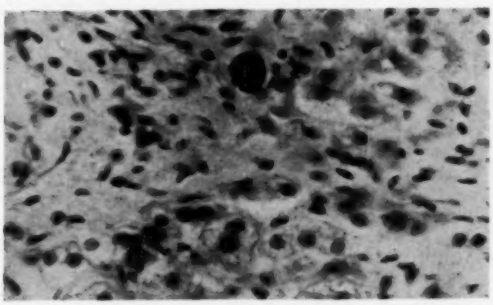


Fig. 14.—Adrenal cortex showing focal calcification. (Hematoxylin and eosin. ×320.)

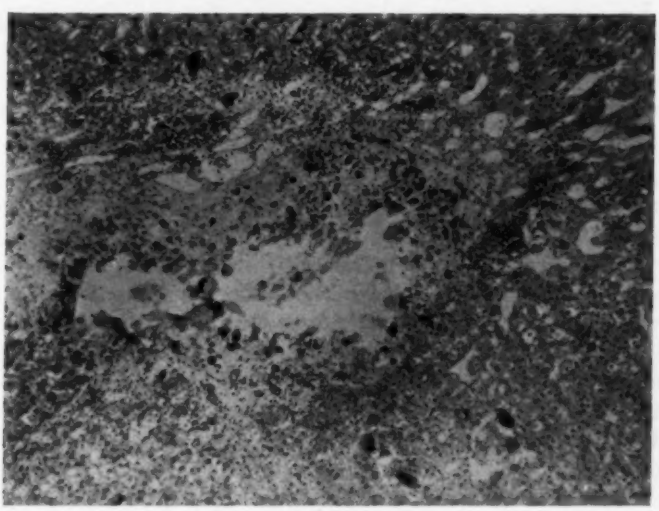


Fig. 15.—Adrenal cortex with large calcific deposit. (Hematoxylin and eosin. ×80.)

In all glands there was some degree of pleomorphism and hyperchromatism of epithelial cells scattered in the fascicular and gomerular layers (Fig. 16). This nuclear variability was much more pronounced than in normal glands. In about 25 per cent of the infants, extremely large, bizarre, epithelial nuclei were observed. These had prominent nucleoli and coarsened nuclear chromatin. A few had irregular, lobulated nuclear borders.

There were microscopic abnormalities of the renal parenchyma in all infants in this group. No essential differences were observed between the kidneys of hydropic or icteric infants or those without external evidence of disease. The amounts of renal pigment were somewhat greater in those infants with icterus.

Generally the glomeruli were normal. In only two patients there was fragmentation of glomerular and glomerular capsular epithelial cells.

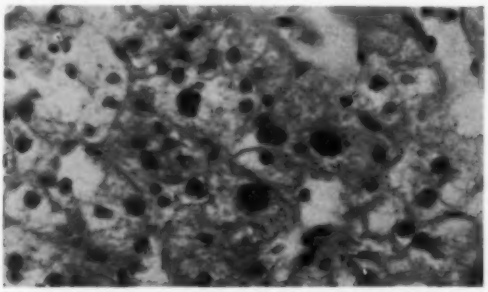


Fig. 16.—Adrenal cortex showing nuclear pleomorphism and hyperchromatism. (Hematoxylin and eosin. ×320.)

In almost all cases there was considerable degeneration of the convoluted tubular epithelial cells; this was considered to be post mortem in part. However, these cells usually contained yellow or brown pigment granules, some of which were stainable with Prussian blue. Pigment casts in convoluted and collecting tubules were numerous. These casts were observed even in nonicteric infants. The color of some casts suggested the presence of hemoglobin.

Vacuolization of the cells of Henle's loop was seen in only one infant.

Hemopoiesis to the extent seen in the liver and spleen was not present in the renal parenchyma. The foci were generally more numerous in the interstitial tissue near the corticomedullary junction.

There was edema of the renal pelvic connective tissue in a few patients. Desquamated pigmented epithelial cells were observed in the renal pelvis of one.

There was extensive hemorrhage, edema, and exceeding heavy infiltration with neutrophilic leucocytes in several of the renal papillae in two infants. Destruction of the collecting tubules with formation of microabscesses was observed in these areas. The overlying pelvic mucosa had desquamated.

A main renal vein of one infant was obstructed by a hyaline thrombus. The peripheral portion of this structure was organizing and was heavily and focally infiltrated with granular calcific material (Fig. 17). The venous wall

was fibrosed and infiltrated with lymphocytes. The smaller tributaries of this vein were recanalized, and calcific deposits were observed in the residual thrombotic material.

Generally the bone marrow of these infants was somewhat more cellular with greater crowding of the cells than seen in normal infants. Usually the nucleated red blood cells were not grouped distinctly as seen in the marrow of normal newborn infants. Immature nucleated red blood cells were predominant and granulocytes appeared diminished. In two icteric infants the marrow contained widely scattered intact hemopoietic cells, separated by numerous faded cellular ghosts. Macrophages containing brown pigment were present in the marrow of many of the infants. Severe sinusoidal congestion near an epiphyseal line had displaced most of the hemopoietic tissue in one patient.

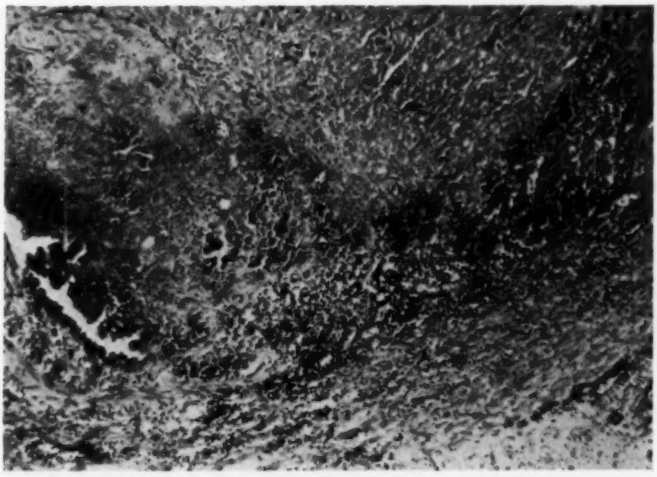


Fig. 17.—Thrombosis of renal vein with calcification. (Hematoxylin and eosin. ×80.)

The lymph nodes usually showed some depletion of lymphocytes. This appeared to have no relation to the degree of hemopoiesis present. Leucopoiesis was observed in the sinusoids of a few nodes. Phagocytosis of red and white blood cells by sinusoidal reticuloendothelium was seen in one lymph node. In one set of icteric twins there was fragmentation of the peripheral lymphocytes, accompanied by neutrophilic leucocytic infiltration. Most nodes contained pigment-filled macrophages in their sinusoids.

Edema and hemopoiesis of a mild degree generally characterized the submucosa of all portions of the gastroenteric tract. In a few instances the lymphoid follicles of the large and small bowel were almost replaced by hemopoietic tissue. There was glandular irregularity with edema and fibrosis in the gastric mucosa of one infant.

The pituitary glands of these infants were not abnormal.

The microscopic alteration of the brain in fifteen of the twenty infants was limited to varying degrees of edema.

A variety of histologic lesions was observed in the brains of five infants with kernicterus. There was more extensive damage in the brains which were diffusely pigmented than in those with only localized nuclear pigmentation. The cerebral basal nuclei and the medullary nuclei were most severely affected. There were increased numbers of glial cells in these areas. Nerve cells in the pigmented nuclei often showed three types of cytologic alteration: (1) The majority had changes considered to be post mortem only in part. Their cytoplasm was finely vacuolated, poorly outlined, and had indistinct processes. There was considerable loss of Nissl substance. Nuclear chromatolysis was common and neuronophagia was observed occasionally. Some cells had disappeared, leaving empty spaces. Pigment was not demonstrated in the cytoplasm of nerve cells in these five infants. (2) Fewer of the nerve cells in the pigmented nuclei had condensed, dark eosinophilic cytoplasm and oval hyperchromatic nuclei. (3) Several small groups of nerve cells were condensed, pyknotic, and heavily impregnated with calcium (Fig. 18).

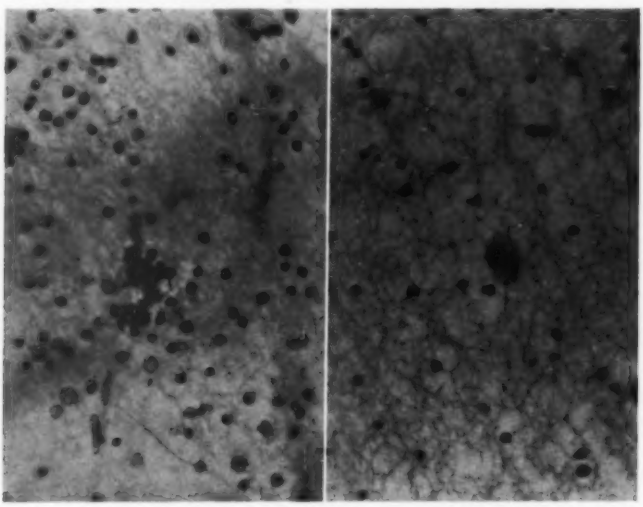


Fig. 18. Fig. 19.

Fig. 18.—Basal nucleus showing cellular necrosis and calcification. (Hematoxylin and eosin. ×320.)

Fig. 19.—Pigmentation of glial cell. (Hematoxylin and eosin. ×320.)

All portions of the brain showed perivascular and pericellular edema. Alterations of the supporting glial tissue was a prominent feature in the two brains with diffuse pigmentation. There was separation of the fibers by edema. The glial fibers, particularly in the basal nuclei, were coarsened. Fine granules and coarse amorphous masses of yellowish-tan pigment lay in the spaces between the glial fibers. Many of the glial cells, especially the oligodendroglial cells, had swollen cytoplasm. There was homogeneous tan staining of the cytoplasm of many (Fig. 19) or fine yellow pigment granules in a few.

The affected nuclei usually showed considerable vascular congestion. Vascular thrombosis was not observed in any of the brains.

Although the gray matter of the spinal cords of two infants was pigmented, microscopic abnormalities or evidences of pigmented deposition were not demonstrable.

COMMENT

It is apparent that the icteric infants, the hydropic infants, and those without external evidence of disease have similar or identical pathologic lesions. In the three types of hemolytic disease described in this paper the lesions differ essentially only in degree, depending mainly on the duration and intensity of action of maternal antibody on the infant's tissues.

Most of the histologic alterations found in this disease result from hemolytic destruction of red blood cells. Icterus of many tissues, including the brain, and deposition of pigment in a variety of organs are prominent features.

Compensatory hemopoiesis occurring in almost all organs and tissues includes the extramedullary production of granulocytes and megakaryocytes, suggesting that leucocytes and platelets, as well as red blood cells, are being destroyed.

Severe injury of the hepatic parenchyma in many of the infants seems related mainly to the degree of hemopoiesis. Thus large masses of proliferating blood cells appear to displace and compress the cords of hepatic cells. Anoxia or even direct action of maternal antibody may also be factors in hepatic degeneration. That the icterus has an obstructive, as well as a hemolytic, component is indicated by evidences of excretion of bile in the urinary tract. Intrahepatic biliary obstruction probably results mainly from distortion of the parenchyma by abundant hemopoietic tissue.

The cause of the degeneration of nerve cells of the brain is not readily explained.[5] Pigment may not be visible in neurons even when the entire brain is heavily pigmented, and neurons may show extensive degeneration without pigmentation. Also abundant pigment lies either between glial fibers or in glial cells. These facts suggest that cellular degeneration and nuclear jaundice may not be directly related. The focal necrosis with calcification resembles closely the similar process in the adrenal cortex. Thrombosis is not a cause of damage of the central nervous system in erythroblastosis.

Other lesions occurring in the thyroid, thymus and adrenal glands, and pancreas are probably not related directly to hemolysis. Their relation to the other lesions remains obscure.

General depletion of lymphocytes in the lymph nodes, thymus gland, and spleen is a common finding in this disease. It is evident that replacement by proliferating blood cells does not explain the reduction of the lymphoid elements although hemopoiesis is occurring in these tissues.

Abnormalities of the adrenal glands, thyroid gland, and pancreas are consistently seen. The adrenal glands of these infants not only lack the neonatal involutionary changes of normal glands but are characterized by lipid infiltration of most of the cortical cells. Usually there is an associated nuclear

enlargement and pleomorphism. Focal necrosis with calcification is not uncommon. Although most of these adrenal changes have been described by several investigators,[1, 2, 3] it has been generally concluded that these adrenal lesions were not entirely characteristic of hemolytic disease. In the group of infants described in this paper the adrenal lesion was one of the most consistent.

Hypertrophy and hyperplasia of the pancreatic islets are fairly consistent findings in erythroblastosis.[1, 2] Although similar enlargement of islets may be found in nonerythroblastotic infants,[4] the islets of infants with hemolytic disease are characterized in addition by nuclear hyperchromatism and pleomorphism. The nuclear abnormalities of both the pancreatic islets and the adrenal cortices are reminiscent of the so-called exhausted Hurthle cells of the adult thyroid gland.[6]

Thyroid hyperplasia was a fairly consistent lesion in the twenty infants. Associated glandular fibrosis in two infants suggested that the hyperplasia was present during fetal life.

SUMMARY

The major pathologic lesions in twenty newborn infants with hemolytic disease have been described and a number of them illustrated. The majority of lesions appear directly related to and secondary to hemolysis of red blood cells.

Other lesions, notably those of the endocrine glands, are present with consistency, even in infants without external evidence of disease. Their relation to the total disease process warrants further investigation.

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A STUDY OF THE OCCURRENCE OF NORMAL Rh-NEGATIVE INFANTS BORN TO SENSITIZED Rh-NEGATIVE WOMEN

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IN STUDYING the occurrence of Rh sensitization in Rh-negative women, thirty instances were found in which normal Rh-negative infants were born to mothers whose sera contained Rh antibodies ante partum. The sample was analyzed according to type and amounts of Rh antibodies present in the maternal serum ante partum, the trend of the antibody titer, the ABO blood groups of both mother and child, and the frequency of ABO compatibility between mother and child. The purpose of this study was to determine whether the birth of an Rh-negative baby could be predicted ante partum in a sensitized Rh negative woman, and whether the women in the sample under consideration might exhibit any specific characteristic in common.

Description of the Sample.—The sample was selected from a series of 250 instances of *sensitized* Rh-negative women whose sera were submitted for Rh antibody tests, and it consists of 30 Rh-negative women, all of whom showed laboratory evidence of Rh sensitization during pregnancy and subsequently bore normal, *Rh-negative* infants.

Analysis of the Sample.—For purposes of analysis, the sample was divided into two categories: Group I, consisting of 17 cases in which Rh antibodies were present in the maternal serum on all examinations, and Group II, consisting of 13 cases in which Rh antibodies were present on some occasions and absent on others. Group I was further broken down into those cases in which the antibody titer increased during the pregnancy by at least two or more serum dilutions, and those cases in which the antibody titer was constant and did not vary by more than one serum dilution; in no instance did the antibody titer decrease in the ante partum tests.

The results of an investigation of selected clinical and immunization data on the sample are given in Table I. It was found that all women of Group I had had at least one previous pregnancy; while in Group II, there were 4 primiparous women. It was not always possible to obtain information concerning the clinical condition of the children previously born to these women, but judging from those in whom the history was obtained, it was found that all 3 of the women of Group I whose history was complete, and who showed a rising Rh antibody titer, had previously borne erythroblastotic infants; and 4 out of 7 of those showing a constant titer had borne afflicted infants. In Group II, there were no indications of previously afflicted infants. Rh antibodies were found on the first specimen examined in all cases of Group I and in 8 of the 13 cases of Group II.

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TABLE I. CLINICAL AND IMMUNIZATION DATA ON 30 SENSITIZED Rh-NEGATIVE WOMEN WHO BORE Rh-NEGATIVE INFANTS

		GROUP I Rh ANTIBODIES CONSISTENTLY PRESENT ON ANTEPARTUM TESTS			GROUP II Rh ANTIBODIES NOT CONSISTENTLY PRESENT
		TOTAL	INCREASING TITER	CONSTANT TITER	
Total		17	7	10	13
Gravidity of mother:	1				4
	2	2	1	1	5
	3	4	2	2	2
	4	6	3	3	1
	5	2	1	1	1
	6	2		2	
	7	1		1	
History of having borne an infant afflicted with hemolytic disease of the newborn:	YES	7	3	4	
	NO	3		3	13
Clinical condition of previous children unknown		(7)	(4)	(3)	
Rh antibodies present in first specimen tested:	YES	17	7	10	8
	NO	0	0	0	5

TABLE II. RESULTS OF Rh ANTIBODY TESTS IN Rh-NEGATIVE WOMEN WHO BORE Rh-NEGATIVE INFANTS

		GROUP I Rh ANTIBODIES CONSISTENTLY PRESENT ON ANTE-PARTUM TESTS			GROUP II Rh ANTIBODIES NOT CONSISTENTLY PRESENT
		TOTAL	INCREASING TITER	CONSTANT TITER	
Total		17	7	10	13
No. of specimens examined per patient	1				
	2				
	3	4		4	
	4	2		2	4
	5	1		1	
	6	5	4	1	4
	7 or over	5	3	2	5
Highest amount of Rh antibody present in ante-partum tests					
	trace (±)				1
	1+	1		1	4
	2+	2		2	8
	3+	2		2	
	4+	12	7	5	
Rh antibodies present in					
saline tests only		1		1	3
albumin tests only		1		1	3
both saline and albumin tests		12	6	6	7
(Albumin tests not done)		(3)	(1)	(2)	
Higher amounts of Rh antibodies in albumin than in saline (higher by 2 or more serum dilutions)	YES	10	5	5	1
	NO	4	1	3	12
(Albumin tests not done)		(3)	(1)	(2)	

The results of the Rh antibody tests were then studied (Table II). Three or more blood specimens were examined in each case. In Group I, all women whose titers increased during pregnancy showed *appreciable amounts* of Rh antibodies (3+ or greater), the highest titer noted being 1:32. Of those whose

titers remained constant, 7 showed appreciable amounts and 3 showed *small amounts* (2+ or less). In Group II, all showed small amounts of Rh antibodies.

Some of the cases in the sample were collected before the Rh sensitization test using bovine albumin was devised[1]; therefore, in three cases, information regarding the presence of this type of antibody is incomplete. Rh antibodies were present in both saline and albumin in all cases with increasing titers and in 6 out of 8 instances of those with constant titers. In Group II, 7 of 13 showed small amounts of antibodies in both the saline and albumin tests.

Since a preponderance of the type of Rh antibody detected by albumin tests is apparently significant in the production of hemolytic disease of the newborn,[2, 3, 4] this feature was also investigated. The women whose Rh antibody titers increased showed definitely higher amounts in albumin than in saline in 5 out of 6 cases, and those whose titers remained constant showed higher titers in albumin than in saline in 5 of 8 cases. Group II showed small amounts of Rh antibodies in all cases and no preponderance of one type of antibody over the other could be established.

The ABO blood groups of mothers and infants are shown in Table III. There appears to be a slight increase of blood group O among the mothers of Group I. Among the infants, the incidence of the blood groups is normal. In Group II, there is a decrease in blood group O in both mothers and infants possibly due to a vagary of the sample, however, none of these findings are statistically significant.

ABO compatibility between the mother and the child occurred less frequently than might be expected[5] in the women whose Rh antibody titers remained constant; in the other two groups the incidence of ABO compatibility was normal.

TABLE III. THE INCIDENCE OF BLOOD GROUPS AND ABO COMPATIBILITY BETWEEN MOTHER AND CHILD IN A SERIES OF 30 SENSITIZED RH-NEGATIVE WOMEN WHO BORE RH-NEGATIVE INFANTS

		GROUP I Rh ANTIBODIES CONSISTENTLY PRESENT ON ANTE-PARTUM TESTS			GROUP II Rh ANTIBODIES NOT CONSISTENTLY PRESENT
		TOTAL	INCREASING TITER	CONSTANT TITER	
Total		17	7	10	13
ABO blood groups of mothers	O	11	5	6	3
	A	5	1	4	7
	B	1	1		2
	AB				1
ABO blood groups of infants	O	8	5	3	1
	A	6	1	5	8
	B	1		1	3
	AB	1	1		1
(Infant not typed)		(1)		(1)	
ABO compatibility between mother and child	YES	11	6	5	11
	NO	5	1	4	2
(Infant not typed)		(1)		(1)	

DISCUSSION

The presence of Rh antibodies in the sera of Rh-negative women bearing Rh-negative infants has been attributed to "anamnestic" responses or "carry-over" titers originally stimulated by a previous Rh-positive pregnancy or a transfusion of Rh-positive blood.[6, 7, 8] A study of this phenomenon is important from the standpoint of predicting its occurrence and possibly in distinguishing this type of ante-partum immunization from that present in women currently undergoing Rh sensitization by an Rh-positive fetus.

The inconsistent presence of small amounts of Rh antibodies found in the subjects of Group II has been considered to be nonspecific. They may be accounted for by variations in technique, unknown contaminations of serum or glassware, and possibly other factors. We also observed similar inconsistent antibody findings in a group of Rh-negative women who subsequently bore clinically normal Rh-positive infants.[3]

In Group I, the rising Rh antibody titers may be regarded as instances of the "anamnestic" response, and the constant antibody titers as instances of the "carry-over" phenomenon from previous Rh immunization. All of the women in Group I showed a high degree of sensitization. Many of them had previously borne erythroblastotic infants, and many demonstrated appreciable amounts of Rh antibodies in their sera with an excess of the type of antibody detected by the albumin test. This is especially true in the group of women whose antibody titers increased during pregnancy, indicating that possibly they were more highly sensitized than those showing constant titers. It is difficult to determine whether the intensity of sensitization is due to greater exposure to Rh-positive blood or greater individual immune response.

In the group of women whose Rh antibody titers remained constant there is a greater incidence of ABO *incompatibility* between the mother and the child than would have been expected normally. In these cases it is possible that the "competition of antigens"[9] kept the Rh antibody titer from increasing; on the other hand, it may have been the greater number of blood group O individuals which influenced the incidence of compatibility.[5]

It is conceivable that a constant "carry-over" antibody represents an acquired serum characteristic in a previously sensitized individual. It is more difficult to understand why, in some instances, such antibodies are stimulated to increase even though the original antigenic stimulus is apparently lacking. The activity of the individual immune mechanism is influenced by such factors as the reactivity of the reticulo-endothelial system[10] and this in turn may possibly be influenced by the metabolic and physiologic changes incident to pregnancy.

At present, the only way in which a prediction of the birth of an Rh-negative infant to a sensitized Rh-negative woman may be made, is to determine the Hr status of the husband, and if he is found to be heterozygous (Rhrh) and if the maternal antibody titer remains constant, the chances are fairly good that the baby may be Rh negative. In instances of previous intense Rh sensitization, the antibody titer may actually rise, thereby making such a prediction impossible.

SUMMARY

1. Thirty instances of normal Rh negative infants born to sensitized Rh-negative mothers were studied.

2. Small amounts of Rh antibodies (2+ or less) occurring *inconsistently* in ante-partum tests were regarded as nonspecific and of no significance.

3. The tests for Rh sensitization showed appreciable amounts of Rh antibodies to be consistently present in the sera of 17 Rh-negative women who subsequently bore Rh-negative infants. In seven instances the ante-partum antibody titer increased in intensity and in ten instances the antibody titer remained constant.

4. All women in whom the antibody titers were consistently present (Group I) showed evidences of a high degree of Rh immunization in terms of the amount and type of antibody present, and in some instances by having previously borne an erythroblastotic infant.

5. The only basis for the prediction of an Rh-negative infant to be borne of a sensitized Rh-negative woman is first, the determination of the Hr status of the husband, and second, the trend of the maternal ante partum Rh antibody titer. If the husband is heterozygous (Rhrh) and the titer remains constant, the baby will likely be Rh negative; however, some highly immunized Rh negative women may actually demonstrate a rising Rh antibody titer and still bear an Rh-negative infant.

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THE SIGNIFICANCE OF NUTRITION AS AN ECOLOGIC FACTOR IN THE PREVENTION OF DISEASE

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HIPPOCRATES, who understood the fundamental importance of the diet, is reported to have stated that "Depletion produces many other evils, different from those of repletion, but just as severe."[1] In the intervening centuries many observations have shown that a relationship exists between diet and such diseases as beriberi, scurvy, rickets, pellagra, osteomalacia, and xerophthalmia. However, it was not until the fundamentals of an adequate diet were defined that the significance of nutrition as an ecologic factor in the cause and prevention of disease could be appreciated. The direct application of the fruits of nutritional research to the prevention of deficiency diseases, which in part result from the conflict of man with his physical and social environments, also focused attention upon nutrition as an ecologic factor in other diseases, such as tuberculosis and diabetes. Malnutrition and undernutrition, often the result of displacements in the social environment, render individuals more vulnerable to the attacking forces of disease regardless of their etiologic agents. Man can make adequate adjustments for all ecologic factors excepting the most important one—his nutriment. He cannot adjust himself to an inadequate, devitalizing diet.

All of the features which make up the internal and external environment are a part of human ecology, which is the study of the adjustment of man to the physical and social environment. The geographic and climatic particularities of an area are important because they determine in great measure the kinds of plant and animal life available for food, the type of clothing needed, and the character of the shelter.

Primitive man—the hunter, the fisherman, and the food forager—spends most of his time in search of food and eats everything he can secure which is edible. Ecologically, primitive man is a child of nature, compelled to accept the inevitable natural environmental forces which act as barriers to his comfort.[2] Experience has taught him which foods to avoid. His diet is *natural*, consisting of the flesh of mammals, birds, fish and shellfish, insects, wild fruits, berries, tubers, roots, bulbs, and nuts. Fish eggs, acorns, and the eggs of wild birds are valuable features of this diet. He lives largely a hand-to-mouth existence because facilities for the preservation or the storage of food reserves are limited. The primitive agricultural peoples became more settled because they could cultivate plants and create reserves of food which resulted in larger and more stable populations. The cereals, the result of intensive cultivation of primitive grasses, were of basic importance in the food supply

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and they conditioned the character of the civilization—corn in the western hemisphere, rice in the Far East, and rye, barley, wheat, and oats in Europe.

Huntington[3] points out that extensive agriculture was impossible until the domestication of draught animals was assured. They were necessary for transportation and the cultivation of the land, and some were used as sources of food and clothing. The milk-producing animals (the cow, mare, goat, and in some areas sheep) played a very important role in the ecology of pastoral and agricultural peoples. With the development of farm machinery, the cultivation of cereals on a large scale became feasible. The steel-faced plow enabled cultivated cereals to triumph over the growth of grass in virgin soils. This achievement ensured both a stable and a reserve food supply, and made possible large urban populations. The storage of whole grains under primitive conditions brought about spoilage which meant waste of reserve food supply. Since a reserve of cereal grains meant freedom from famine, ways and means to conserve them were developed which resulted in refining and purification with their consequent sacrifices of natural nutritional substance. The significance of the losses could not be evaluated until the fundamental nature of the nutritional elements could be defined. It was not possible to discover the nature of the vitamins by the methods of routine chemical analysis. It was necessary for the technique of biologic experimentation to be perfected and the science of biochemistry to be established before the presence and functions of these accessory food factors could be determined. The modern knowledge of nutrition may be said to have been initiated in the second decade of this century by the experimental evidence that there were substances in food, later called vitamins, which were essential to life. During the past thirty-five years most of the essential factors of food have been discovered and isolated, yet we are increasingly aware that food as it occurs in nature contains a better balance of identifiable substances, in addition to the other activators, than can be formulated artificially.

The large cities of ancient civilizations were political creations, whereas the modern great cities are the products of economic-geographic factors. In 1790, about 3 per cent of the American people lived in urban communities, whereas in 1930, more than 65 per cent of the people of the United States lived in cities of more than 2,500 inhabitants. During the same period, England increased its urbanization from about 25 to more than 80 per cent of the population, a result of the industrial revolution which not only changed the character of the food supply, but created new ecologic factors in the physical and social environment of the people. Today comparatively few urban people have gardens or domestic animals to supply meat, milk, and eggs. Hunting and fishing as a real source of food is impossible in an industrialized area, such activities are primarily for sport and the food secured is incidental. Most people are totally dependent upon the money they earn in order to buy food and other necessary supplies, which from the standpoint of human ecology is a rather new feature in world history.

Civilization demands that man establish intricate relationships with his physical environment. This means that his social environment becomes ex-

tremely complicated because the higher the civilization, the greater is the demand for the products of labor which are associated with what we know as the standard of living of the group. Steam transportation was probably the first big change in the physical and social environment which altered the lives of the people on a world-wide scale. More rapid transportation made possible a greater distribution of food and other articles of trade, and a greater migration of peoples than could be accomplished by the earlier modes of travel. Certain diseases among which were cholera, plague, typhus, dysentery, and smallpox became more widespread because they were introduced into new places along the trade routes. In the past two centuries the changes in transportation, industrialization, housing, sanitation, communications, education, agricultural techniques, refrigeration, etc., have influenced the ecologic significance of the external and social environments. These changes have brought about not only a different but also an *altered* food supply from that known to primitive man. With the growth of modern cities and the complexity of the social organizations necessary to urban living, the handling of perishable foods—milk, eggs, meats, fruits, and vegetables—creates problems not only of transportation and refrigeration, but also of public health.

Our complex civilization is dependent upon many interrelationships between ecologic factors in the physical and social environments. One of the functions of ecology is to remind us that civilization is dependent upon a constant and predictable food supply. Our food chain, although fundamentally the same as that of primitive man, is more devious and complicated. Like all other animals, man is ultimately dependent for his food upon plants, which take the raw materials of the earth and air and synthesize them into a form which can be assimilated and utilized as essential material for growth, repair, and regeneration.

For several centuries physicians associated deficiency diseases with aberrations of the diet or hygiene, but their experiences were so varied and their knowledge so conjectural that uniformity of opinion concerning the true etiology could not be adduced. They could not explain their therapeutic successes or failures because they did not know the nutritional or dietary properties of the foods which were used as remedies. It may be said that the inordinately long and discouraging past history of the deficiency diseases is an example of the inability of man to solve nutritional problems by the trial and error method of human experience alone. Gamble[4] stated: "This splendid significance of the results of recent studies of rickets is not in the least subtracted from by admitting that the knowledge thus gained is not new knowledge. That cod liver oil would cure rickets has been known for several hundreds of years. This discovery is credited to fisher folk of northern Europe. That sunlight is preventative was convincingly evident to students of rickets generations ago. In recent times, however, the introduction into medicine of a commendably cautious attitude of reliance only on directly demonstrable data has produced a perhaps too inclusive disrespect for the older empirically established beliefs. A splendid clearance of rubbish has been accomplished but, inevitably, grains of gold have been lost with the dross. To an even mildly critical attitude of mind the belief that oil from the liver of codfish is specifically curative of a human ailment was

obviously a quaint bit of archaic medical lore. The theory of a relationship of sunlight to prevention seemed an interesting but intangible surmise. The scientific method of thinking having produced skepticism, it was quite necessary that the rickets-preventive action of cod liver oil and of sunlight be rediscovered in irreproachably scientific terms. That this has been most beautifully done ensures a permanent and active belief in the efficacy of these agencies. And since their employment is so easily practicable we may now regard rickets as a preventable and unnecessary disease."

From the standpoint of preventive medicine the advancing knowledge of nutrition perhaps plays its greatest role in the field of pediatrics. Rickets and scurvy, until recently scourges of infants and young children, were seldom the direct cause of death, but they played their insidious roles by undermining the health of children which in turn made them more vulnerable to intercurrent communicable diseases. The early pediatricians realized that raw and natural foods in the diet were often helpful, and many, including Cheadle[5] in the late nineteenth century, recommended the use of the certain foods to prevent scurvy, such as vegetable juices, orange juice, grape juice, fresh peaches, fresh milk, raw meat juices, raw scraped beef, and cooked potato pulp. Some children were not cured on such a regimen, but the pediatricians did not realize that the fault lay in the content of vitamin C, since natural foods vary in their content of the vitamin or may lose it through improper handling.

Rickets was associated with fat starvation, and the method of treatment was to use cream and cod liver oil. Inasmuch as the vitamin D content of cod liver oil was not at that time assayed, the possible good effect of the vitamin was counterbalanced by the potential bad effects of diarrhea and dehydration following the high fat diet. Since the results of treatment with these fats were not uniform, pediatricians were in disagreement as to the value of them, even though some children were markedly improved by their use. Likewise, sick children were sent to the country where they could enjoy fresh air and sunshine, but the reasons for the beneficial effects could not be explained. Artificial feeding did away with many of the social and economic problems of the wet-nurse, but new physiologic and pathologic problems were brought about by the artificial preparations used for infant feeding. Clinical experience demonstrated, by and large, that some natural foods were necessary in the diet of the infant and young child, but it was only after the vitamin hypothesis was established and bacteriology had explained the problems involved in the spoilage of foods that the empirical knowledge of the nineteenth century pediatricians could be explained. Handler[6] recently stated: "It is amusing perhaps, that with all the information concerning the role of nutrition in the etiology of pellagra gained in the last three decades, the advice of Italian physicians, two centuries ago, to eat well of milk, meat, and greens and sparingly of corn cannot be improved upon."

Research in nutrition has furthermore made possible an analysis of the ecologic factors in the physical and social environments which determine the racial and regional food habits of man when survival depends upon the food supply of the immediate environment. The importance of nutrition in the

maintenance of the finest characteristics of animal species is well understood and objectively applied. Insofar as the human being is concerned, we do not apply our knowledge intelligently, although we are aware that in order to enjoy optimal health the human subject must be well nourished—food is the best medicine.

The prevention of malnutrition and the deficiency diseases concerns more than a knowledge of the dietary properties of foods. Beri-beri and pellagra are still endemic in many regions of the world; while frank rickets, scurvy, and even xerophthalmia are occasionally seen in the medical clinics. The biologic conditioning of individuals from a nutritional standpoint takes place so slowly that only the trained observer can perceive the subtle changes while they are developing and design methods of detecting them. Full-blown deficiency diseases are spectacular and easily recognized, but they do not indicate the whole story. It has been said that "pellagra accepted as a nutritional disease is of less importance in its own right than as an index of dietary conditions in the locality."

The extensive use of highly refined foods results in devitalized individuals, many of whom are overweight due to water-logged tissues. Malnutrition in the midst of plenty leads to "human erosion" or "hidden hunger," brought about by the poor selection of food, due to lack of knowledge of food values, the over-use of highly purified products, dislike of certain foods, or because of economic factors. The most important nonspecific element of immunity is a diet rich in vital proteins, in order to form a bulwark of resistance to devitalization, disease, and disintegration. Other features of the social environment such as poor housing, chronic fatigue, emotional unrest, and anxiety make these individuals vulnerable to many illnesses and their recovery is slow because the body's recuperative powers have long been undermined by an inadequate diet and poor physical and mental environment.

Too many individuals take an inadequate diet and thereby suffer from nutritional deficiencies. In 1943, the National Research Council[7] reported that inadequate diets are widespread and mild nutritional deficiency abounds throughout the nation. The ecologic factors conditioning the habits of life, especially those dealing with nutrition, are of cardinal significance and of paramount importance in assessing the health program of a human population. According to Burnet and Aykroyd[8] "nutrition is an economic, agricultural, industrial and commercial problem as well as a problem in physiology." We would like to add that it is also a problem in bacteriology, immunology, education, sociology, and geography with special reference to water, soils, temperature and climate—all of which makes nutrition the foundation stone of human and medical ecology.

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STATUS MARMORATUS: A FORM OF CEREBRAL PALSY FOLLOWING EITHER BIRTH INJURY OR INFLAMMATION OF THE CENTRAL NERVOUS SYSTEM

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IN SPITE of considerable investigation, cases of so-called congenital cerebral infantile paralysis still present many problems of differential diagnosis, pathogenesis, and etiology. How many of these conditions are actually congenital and how many are due to factors acquired at or shortly after birth is not always clear. For, in either case, almost identical clinical pictures often result. Nevertheless, the pathological findings can be distinguished sharply between anomalies of cerebral development on the one hand and lesions resulting from disease processes on the other. Thus, in a series of seventy cases clinically diagnosed as cerebral palsy, I noted that pathologically they were about equally divided into the aforementioned two groups. Among these were fifteen cases who showed a specific neuropathological picture, known in the literature as status marmoratus or marble state. Since the etiology and pathogenesis of this condition has remained controversial, it is my purpose to review the findings in these cases with the hope that such a large material might throw further light on the nature of the disorder.

Status marmoratus was first described by C. Vogt[1] in 1911, and up to 1947 approximately thirty-six cases have been reported. Clinically, the disease manifests itself from earliest infancy and is characterized principally by spasticity and involuntary movements in the form of bilateral choreoathetosis combined with variable manifestations of mental retardation, epileptic seizures, and other less common signs. Pathologically, the distinctive feature is the marbled appearance of the basal ganglia. Marcroscopically, the uniformly gray color of the normal corpus striatum (caudate and putamen nuclei) is broken up by a network of white streaks resembling marble. Microscopically, normal nuclear masses of the basal ganglia are separated by areas containing fine medullated nerve fibers associated with disappearance of nerve cells and proliferation of glial elements. At times, other regions of the brain, notably the thalamus and cerebral cortex, have been found to be similarly involved. Etiologically, various theories have been advanced. While the Vogts, and more recently Alexander,[2] considered the condition to be a prenatal malformation, other authors (Scholz and collaborators,[3] Lowenberg and W. Malamud,[4] Meyer and Cook,[5] and Norman[6]) favored exogenous causes, such as birth trauma and inflammatory processes.

REPORT OF CASES*

History.—Our fifteen cases have been classified into Groups A and B on the basis of two different types of history and are summarized respectively in Tables I and II.

From the Langley Porter Clinic, University of California Medical School.

*The staff of Sonoma State Home and of Pacific Colony, California, cooperated in furnishing this material.

TABLE I—GROUP A

CASE NO.	AGE AT DEATH (YEARS) AND SEX	BIRTH AND EARLY HISTORY	PERMANENT CLINICAL SIGNS AND SYMPTOMS
1 (120)	2 1/2 M	First child. Full term. Instrumental. Spells of apnea and cyanosis; in oxygen tent for several days. Vomiting. Immobility and spasticity.	Spastic quadriplegia with hyperactive reflexes and ankle clonus. Tonic seizures. Microcephaly. Idiocy.
2 (598)	4 1/2 M	Second child. Full term. Precipitate delivery (labor ½ hour). Tonic seizures.	Spastic quadriplegia with hyperactive reflexes and ankle clonus. Jacksonian seizures. Microcephaly. Idiocy.
3 (718)	7 1/2 M	First child. Premature (8 months). Prolonged labor (9 days); large doses of Pituitrin used. Tonic seizures. Dysphagia.	Spastic quadriplegia. No pyramidal signs. Athetoid movements of both arms. Tonic seizures. Idiocy.
4 (956)	8 F	Third child. Full term. Precipitate. Cord around neck. Resuscitation with difficulty. Tonic seizures.	Spastic quadriplegia. No pyramidal signs. Bilateral strabismus. Tonic seizures. Idiocy.
5 (2163)	27 M	First child. Full term. Instrumental (maternal dystocia). Immobility, spasticity.	Spastic quadriplegia. No pyramidal signs. Epileptic seizures. Borderline intelligence (I.Q. 77).
6 (1265)	4 1/2 M	First child. Full term. Prolonged labor (18 hours). Instrumental with trauma to head. Resuscitation with difficulty. Tonic seizures.	Spastic quadriplegia. No pyramidal signs. Bilateral athetoid movements of arms and legs. Tonic seizures. Idiocy. Ossified hematoma of right parietal region.
7 (1270)	1 4/12 M	Full term. Instrumental with considerable molding of head. Prominent caput succedaneum and ecchymosis of orbit on left side. Listlessness, stiffness of neck, right hemiparesis, and left internal strabismus.	Spastic quadriplegia. No pyramidal signs. Involuntary tremor of head and neck. Idiocy.
8 (1465)	13 F	First child. Full term. Prolonged labor (48 hours). "Abnormal position" of child. Epileptic seizures.	Spastic quadriplegia. No pyramidal signs. Athetoid movements of upper extremities. Equinovarus deformity of left foot. Idiocy.
9 (2163)	1 8/12 M	Membranes ruptured 2 weeks prematurely, labor 4 days later, delivery precipitous. Asphyxia for 10 minutes. Tonic seizures.	Spastic quadriplegia. No pyramidal signs. Bilateral athetoid movements. Epileptic seizures. Idiocy.
10 (1324)	7 F	Third child. Full term. Difficult labor. Symptoms since birth.	Spastic quadriplegia. Epileptic seizures. Idiocy.
11 (1800)	8 M	First child. Precipitate (labor ½ hour). Symptoms since birth.	Spastic quadriplegia. No pyramidal signs. Bilateral athetoid movements. Petit mal seizures. Idiocy.
12 (1603)	56 F	Full term. Difficult labor.	Spastic quadriplegia. No pyramidal signs. Bilateral athetoid movements. Explosive speech. Deafness. Moron intelligence (I.Q. 50).

The cases comprising Group A included twelve patients, all having in common a history of some form of birth trauma. The significant factors noted in the various birth histories were prolonged or difficult labor, dry labor, instru-

TABLE II—GROUP B

CASE NO.	AGE AT DEATH (YEARS) AND SEX	BIRTH AND EARLY HISTORY	PERMANENT CLINICAL SIGNS AND SYMPTOMS
13 (820)	1 10/12 F	Second child. Full term. Normal birth and early development. At age of 2 months acute illness characterized by temperature elevation to 103° F., meningeal and cranial nerve signs, and 180 cells in C.S.F.; diagnosed by smear as pneumococcic meningitis, Type B4. Improvement from acute meningitis after two weeks with sulfadiazine and penicillin but permanent sequelae set in.	Spastic quadriplegia. No pyramidal signs. Microcephaly. Idiocy. Epileptic seizures. Death in status epilepticus.
14 (2031)	2 1/2 M	Birth and early development normal. At age of 3 months developed influenza ("flu virus X") associated with fever, vomiting, diarrhea, generalized muscle twitchings and hemiparesis on the left, and deviation of eyes to right. 282 cells and increased protein in C.S.F. but no growth on culture.	Spastic quadriplegia. No pyramidal signs. Bilateral athetosis. Epileptic seizures. Idiocy. Fluctuations of temperature from 98° to 108° F. and death from "central" hyperthermia.
15 (1112)	9 F	First child. Full term. Normal birth. At age of 3 days developed temperature of 109° F. associated with epileptic seizures.	Spastic quadriplegia with hyperactive reflexes and bilateral Babinski's sign. Idiocy.

mental delivery, precipitous birth, prolapsed cord, and prematurity. These factors occurred either singly or in various combinations, but no single one of them was apparently specific. Instrumental delivery characterized four of the twelve cases, in two of which there were external signs of head injury. A period of asphyxia neonatorum of varying duration was commonly observed but evidently accompanied the other factors and did not appear to be an independent process. In a few instances the history was meager, merely stating that there was a difficult or prolonged labor. Such general terms do not necessarily signify birth trauma since they are also frequently mentioned in the birth histories of cases of cerebral agenesis, where obviously injury does not play a role. However, such presumptive evidence of birth injury was further substantiated by the occurrence of acute neurological symptoms immediately following birth. Thus, in almost all of our cases there were either instantaneous tonic or epileptic seizures, states of decerebrate rigidity, signs of cranial nerve meningeal and pyramidal tract involvement, or of increased intracranial pressure. Such signs, when combined with a characteristic history, make the assumption of intracranial trauma incurred at birth seem very probable.

There were three cases comprising Group B. In all of these patients, birth and early development were normal but, following a free interval, signs of acute inflammation of the central nervous system marked the onset of the neurological disorder. In Case 13, there was a proved pneumococcic meningitis, in Case 14 a meningitis or meningoencephalitis associated with "flu,"

and in Case 15 there was a history of a febrile illness accompanied by epileptic seizures. While the latter case probably belonged to this group, there was no conclusive evidence of it.

The family history was negative for nervous and mental diseases in all of the patients with the exception of Case 4. In the latter instance two of the patient's siblings were also noted to be spastics but in each there was a similar history of difficult labor.

Clinical Features.—The permanent sequelae, as summarized in Tables I and II, were essentially similar in the two groups irrespective of the different histories. Spastic quadriplegia was present in all of the fifteen cases. In eight of these there were involuntary movements, chiefly in the form of bilateral athetosis. Of the seven remaining cases, four showed spasticity without pyramidal signs, implying rather a rigidity of extrapyramidal type, while three cases showed spasticity associated with pyramidal signs. Thirteen of the fifteen patients were idiots, one was of moron and one of borderline intelligence. In eleven patients, seizures of one type or another persisted during life. Such variations in the clinical picture depended on differences in localization of the lesions, as will be discussed later. Once the disease became established, the condition appeared to be stationary and death usually occurred from some intercurrent infection.

Pathological Features.—The lesion common to all of the cases was the characteristic marble state and the precise bilateral localization in the striate area of the brain. This occupied most frequently the rostral parts of the putamen and caudate nucleus, particularly the dorsolateral area of the former. Grossly, the lesions appeared as whitish flecks interspersed in the atrophied basal ganglia (Fig. 1). Stained sections with Holzer's method for glial fibers (Fig. 2) demonstrated dense bands of heavily stained fibers usually ramifying from the dorsal region of the striate body and becoming finer as they approached its ventral area. Under higher magnification (Fig. 3*A*), the glial fibers which were frequently perivascular in location, formed an interlacing network, separating unstained normal areas. With Nissl's thionin method for nerve cells (Fig. 3*B*), the fibrous areas were found to be devoid of neurons but containing abundant glial nuclei; occasionally scattered nerve cells showed sclerosis and calcification. With Weil's method for myelin sheaths (Fig. 3*C*), fine medullated nerve fibers were seen coursing through the acellular foci. They corresponded in location and pattern with the glial bands but were frequently less intense than the latter. There was nowhere any evidence that the lesions were still active and it was obvious that they were glial scars, representing an end stage of some disease process. The only unique features were the peculiar marbled pattern of the scars and the paradoxical presence within them of myelinated nerve fibers. In keeping with the view that the status marmoratus was essentially scar formation was the frequent coexistence of other types of lesion. These were either focal or diffuse areas of gliosis without a marbled pattern or cysts of varying size containing remnants of necrotic tissue.

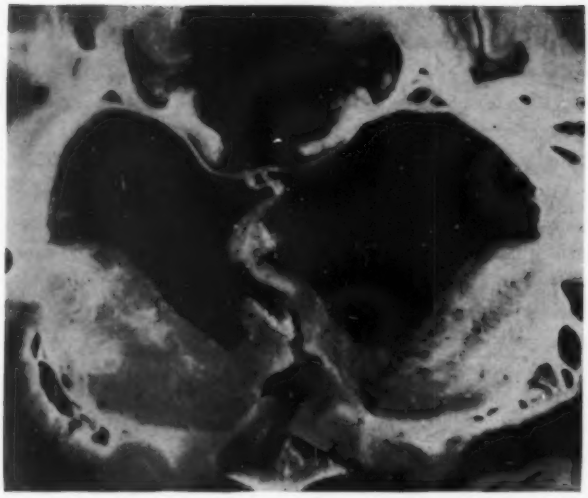

Fig. 1.—Gross appearance of status marmoratus in symmetrical dorsolateral areas of striate body, accompanied by diffuse atrophy and cysts in surrounding structures (Case 7).

Fig. 2.—Status marmoratus in caudate, putamen, and overlying cerebral cortex; diffuse gliosis of intervening white matter. (Holzer glial fiber stain ×5) (Case 7.)

Analysis of the distribution of the lesions showed that besides the striate area, many other regions of the brain were frequently involved, whether in the form of marbled patterns, diffuse atrophy and gliosis, or cyst formation. The putamen was severely and bilaterally involved in all of the fifteen cases.

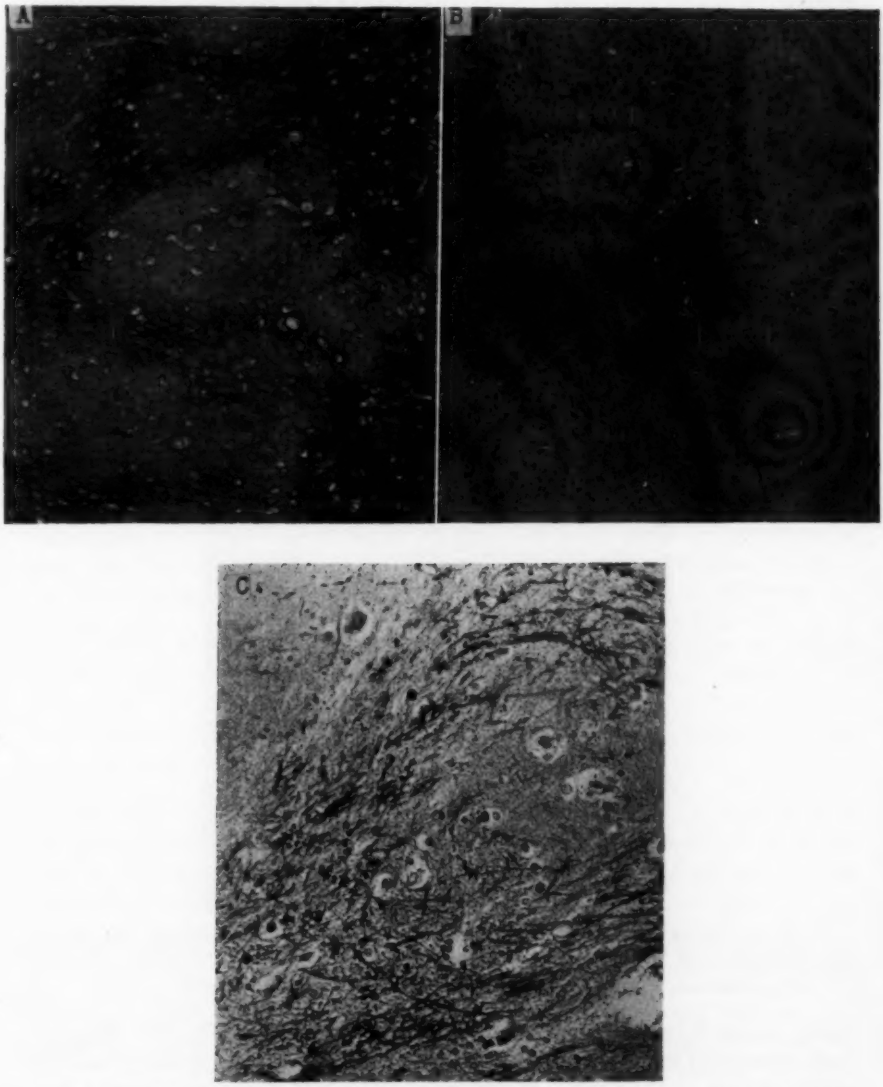

Fig. 3.—Corresponding sections of caudate nucleus showing: *A*, Network of fibrillary gliosis between clear normal areas. (Holzer stain, ×60.) *B*, Foci devoid of neurons and containing proliferated glial nuclei. (Nissl stain, ×60.) *C*, Medullated nerve fibers within acellular foci. (Weil's myelin sheath stain, ×75) (Case 7.)

The globus pallidus was also invariably affected, but usually to a much more moderate degree. The caudate nucleus was involved bilaterally in eleven cases, unilaterally in one and not at all in three cases. From a physiological standpoint, it was of interest that in the four cases with unilateral or bilateral sparing of the caudate nucleus there were no athetoid movements, merely spasticity. In three other spastics without athetosis, the pyramidal tracts were also degenerated. Such findings would imply that athetosis results only when the caudate nucleus is bilaterally involved and where the pyramidal tracts remain intact. The thalamus (Figs. 4 *A* and 4 *B*) was severely and bilaterally involved, usually in the form of status marmoratus, in thirteen

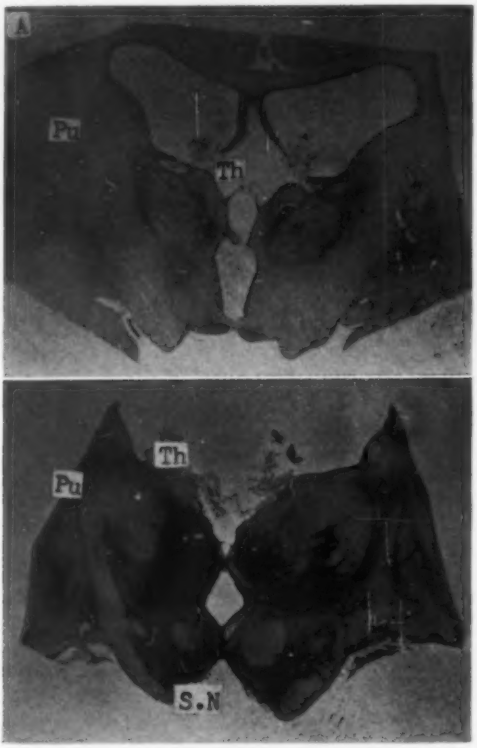

Fig. 4.—Comparison of status marmoratus in thalamus and putamen between *A*, case following birth trauma (Case 6) and *B*, case following meningitis (Case 13). Note also dense gliosis of substantia nigra in latter instance. (Holzer stain.)
Th = thalamus; Pu = putamen; S.N. = substantia nigra.

cases, mildly in one (Case 12) and entirely spared in one (Case 5). The cerebral cortex and white matter were severely affected in eight cases, resulting in gross atrophy of the brain. It was noteworthy that idiocy was present when either the cortex or thalamus, separately or in combination, was severely involved, while in the two cases of moron to borderline intelligence neither

regions were affected to any noticeable degree. This would suggest that degeneration of the thalamus, when occurring in infancy, may be equally responsible for derangement of mental function as in the case of degeneration of the cerebral cortex. Cerebellar lesions of a patchy and mild degree were noted in all cases where epileptic seizures occurred. Such a change is known to occur in various forms of epilepsy including the idiopathic variety and, therefore, not of fundamental importance in status marmoratus. Other areas, less constantly involved were the subthalamic body in four instances, the substantia nigra of variable degree in four, the amygdaloid nucleus in two, and the mammillary bodies in two cases. It may be significant that while the pathology was otherwise essentially similar in Groups A and B, the substantia nigra was most severely involved in the two cases with a history of an inflammatory disorder (Fig. 4*B*). For it is well known that this area is particularly likely to undergo scarring in cases of encephalitis.

COMMENT

Based on the above study several conclusions may be drawn. Status marmoratus is apparently not a disease entity, as originally assumed by the Vogts. Clinically, there is no evidence of a system disease and, although extrapyramidal signs are prominent, mental defect, pyramidal signs, seizures, and other manifestations are also common. Pathologically, although the lesions may be limited in some cases to the striate area, thalamic, cortical, and other regions are also frequently and severely involved. The lesions are without a doubt scars characterized by foci of degeneration and sclerosis and may, therefore, be interpreted as sequelae of an acquired disease process. Much attention has been paid to the phenomenon of hypermyelinization of the scars and on its interpretation depend the divergent views held by various authors. Recently Alexander advanced the opinion that this represents an anomalous frontopontile tract which has been displaced from its normal course during development. Based on this observation, Alexander interprets the disorder as a congenital malformation. The majority of authors, however, are of the opinion that hypermyelinization is a phenomenon of regeneration within a scar, a finding peculiar to the immature infant's brain. From an etiological standpoint, the concept of a prenatal malformation can also be dismissed. There is no evidence of hereditary transmission and in the few instances reported of familial occurrence (as in our Case 4) the role of acquired factors in the siblings can be demonstrated. Two such factors stand out prominently in the histories of our cases, namely, birth trauma and inflammation of the central nervous system. By far the majority of our cases, namely, twelve, can be attributed to some form of cerebral birth injury. As mentioned before, this has already been noted in isolated cases by Meyer and Cook, Scholz, and Norman, and our larger material reaffirms this contention. It is noteworthy that the same factors which operate to produce other types of cerebral lesions induced by birth trauma (Schwartz,[7] Benda[8]) apply to our cases as well. Moreover, such lesions as mantle sclerosis, cystic degeneration, and diffuse patchy devastation observed by Benda in his material of cerebral birth injuries were frequently noted by us, too. On the other hand,

our three cases of inflammatory origin are equally significant and correspond to similar cases reported by Scholz, Lowenberg, and Malamud. However, no specific form of meningitis or encephalitis can be held responsible. It would seem, therefore, that both trauma and inflammation could produce the condition

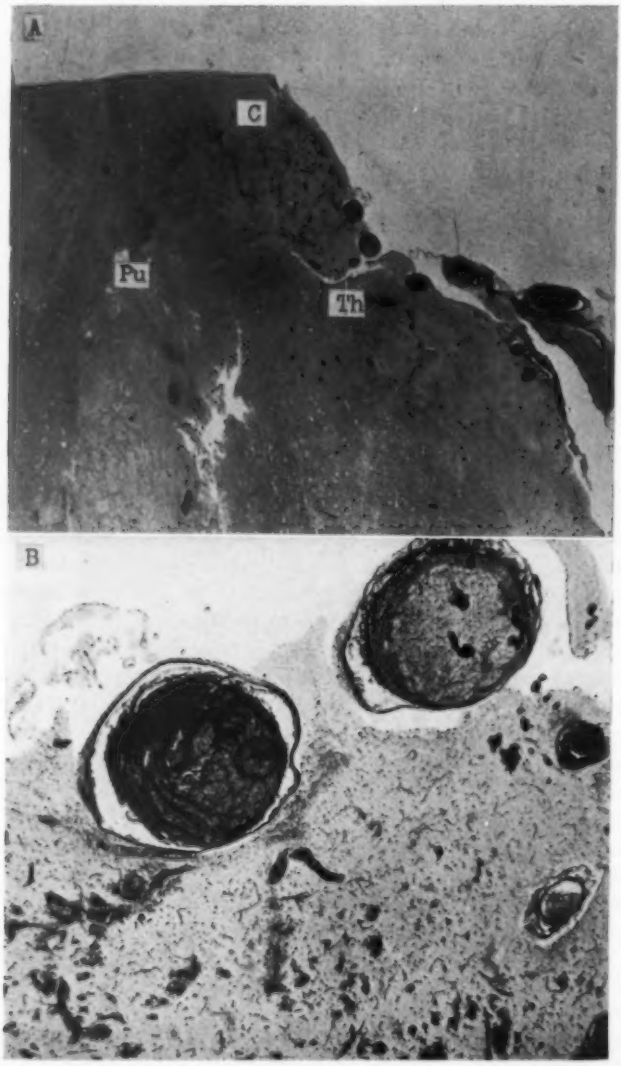

Fig. 5.—Acute thrombosis in tributaries of vein of Galen. *A*, Petechial hemorrhages in caudate; mottled appearance of putamen and thalamus due to foci of anemic necrosis. (Hematoxylin Van Gieson stain, ×4.)

C = caudate; Pu = putamen; Th = thalamus.

B, Higher magnification of venous thrombi and perivenous hemorrhages in caudate. (Hematoxylin Van Gieson, ×50.)

of status marmoratus and that the latter does not depend on a specific cause but rather on a similar pathogenesis.

The particular mechanism of the marbled pattern of the lesions and their tendency to localize predominantly in the striate and thalamic regions still remain unsolved. It has been suggested by some observers (Schlesinger,[9] Meyer and Cook, and Norman) that the distribution of the lesions correspond to the venous drainage area of the Galenic system, viz., the basal ganglia and the subependymal cerebral white matter. If this view is correct, cases of acute thrombosis of these veins might help to explain the pattern of marble state. Such a case of acute marantic thrombosis of the internal veins is illustrated in Fig. 5. It may be seen that the caudate nucleus and the adjacent dorsal parts of the putamen and thalamus are the sites of petechial hemorrhages and foci of anemic necrosis, which follow the course of the venous tributaries of the Galenic system. This corresponds fairly accurately with the main distribution of the lesions in status marmoratus. Under conditions of birth trauma, the Galenic system is particularly vulnerable to stretching, kinking, or thrombosis, as demonstrated by Schwartz. It is, however, more difficult to interpret the pathogenesis of such lesions occurring under conditions of acute meningitis or encephalitis, a problem requiring further investigation. It may be that in such infections either a thrombophlebitis or a coincidental circulatory disturbance involving the Galenic system may occur.

SUMMARY

1. A general survey of the findings in fifteen cases of status marmoratus is presented.

2. A history of birth trauma in the majority of cases and of meningitis or encephalitis in a few instances represent the outstanding etiological factors.

3. The clinical and pathological findings are at variance with the concept of a disease entity.

4. The specific marbled pattern of the lesion is considered as the effect of some disturbance in the Galenic venous system, at least in cases of birth trauma.

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THE BORDERLINE SCHICK TEST

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SOME sixty-two years ago Roux and Yersin[1] discovered that the filtrate of a culture of diphtheria bacilli, free of living organisms, was poisonous, accounting in part for the nature of diphtheria. It was only a step from this to the discovery of antitoxin. Not long after, Erhlich, in the course of quantitative studies, noted that toxin which had been rendered harmless with chemical treatment did not necessarily lose its power to combine with antitoxin, nor, as Ramon so adequately demonstrated later, did it lose its power to stimulate the formation of antitoxin.

Between Ehrlich's work at the turn of the century and Ramon's contributions in the third decade came two other discoveries, a skin test worked out by Bela Schick in 1913,[2] and toxin-antitoxin mixture, an outgrowth from several suggestions, put into action by Park and his co-workers shortly after the Schick test was made available. In the establishment of the Schick test there was an element of luck. There also occurred a basic error. An understanding of the luck and the error may improve our knowledge of the scale of reactions in the Schick test.

Injection into the skin of the amount of toxin required for a practically useful Schick test might well have produced unduly severe reactions in persons with no ability to withstand the toxin. Large intramuscular doses of toxin have been given, inadvertently, with fatal results. Overdoses, given inadvertently for the Schick test, have been followed by severe reactions. Even with a normal dose, the combination of a strong reaction with a high degree of hypersensitivity can be fairly disturbing. The residual local anesthesia which follows some reactions is mute testimony to the possibilities. Park[4] claimed that a variation of 25 per cent in toxicity either way was a maximum tolerable variation. That a dosage governed by a threshold of safety should have a useful meaning in terms of immunity may be called fortuitous.

The Schick test is supposed to divide people into two groups, those who react and those who do not react. We presume that those who react are susceptible and that those who do not react are immune. That the test should be so neatly positive or negative, meaning what we wish it to mean, is stretching a belabored science. By chance, the result has been practically useful, but why?

The scale of immunity to diphtheria ranges from complete susceptibility to a solid immunity signified by absence of infection on repeated exposure. On this scale there are intermediate degrees of immunity, seen, for example, in potentially infected carriers, in persons who have mild or atypical cases, and in persons who survive all except heavy exposure.

From the University of California School of Medicine.

Although we do not know how antitoxin might prevent *infection*, we make a second naïve assumption, presuming that the antitoxin content of the blood serum is directly proportional to the immunity. In some persons there may be one or more units of antitoxin per milliliter of serum, but a large percentage of the population has less than $\frac{1}{10}$ unit.[3] We assume that we measure the immunity by measuring the antitoxin concentration which we assume to be measured by the Schick test. Meanwhile, the scale of the Schick test ranges from severe inflammation to no reaction. The range of severity in skin reactions corresponds to some range in content of antitoxin, but, as we shall see, in no predictable manner.

With the Schick test, we are concerned with comparisons of three scales, as indicated in Chart 1. The simplest base line for comparison is the range of concentrations of antitoxin—a long range. The potential concentration of antitoxin in human serum greatly exceeds our point of interest. There is no reason to suppose that a person with one unit of antitoxin will resist infection any "better" than one with $\frac{1}{20}$ unit. However, there are many persons whose antitoxin is less than $\frac{1}{20}$ unit.

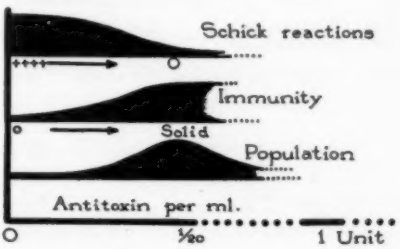

Chart 1.—Relationships between antitoxin content, Schick reaction, and immunity.

The scale of Schick reactions corresponds approximately to a range of antitoxin between $\frac{1}{20}$ and $\frac{1}{500}$ unit per milliliter of serum. At one end of this range we can be fairly sure of susceptibility and at the other end immunity is probable. That there should be a moderately successful partition between susceptible and immune persons based only on antitoxin, and that a safe dose of toxin, in the Schick test, should stand at the threshold in this partition, is almost too neat to believe. We should not believe it too quickly. It is not popular to teach that a *moderate* Schick reaction might mean a *moderate* degree of immunity and a fair chance to escape infection. Medicine does not like gradient scales; yet the sharp decisions demanded by medicine cannot be met unless the facts justify it.

Schick tests consist of the injections of tenth of milliliters in which, in different lots of the product, different amounts of bacterial filtrates are present. Each, however, contains just $\frac{1}{50}$ the amount needed to kill a guinea pig under standard conditions. The amount of filtrate used to prepare the product is determined by the *lethal* activity of the filtrate. The relative volumes of the

minimum lethal dose for the animal and $\frac{1}{50}$ of that volume, used in the Schick test, are indicated in Chart 2. Another volume is also indicated, an amount which likewise kills a guinea pig under similar conditions, but only after it is mixed with a unit of antitoxin. This amount of toxin, familiarly the L+ dose, is as necessary to us in understanding the Schick test as it was to Ehrlich when he discovered that filtrates alike in toxicity might differ widely in their powers to combine with antitoxin. In all toxic filtrates some toxin, an unknown portion, has changed to toxoid, retaining all of the properties of the original toxin except the toxicity. A toxic filtrate, crudely called "diphtheria toxin," contains toxin molecules and toxoid molecules.

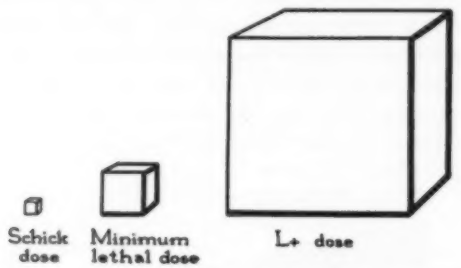

Chart 2.—Volume relationships (in terms of filtrate).

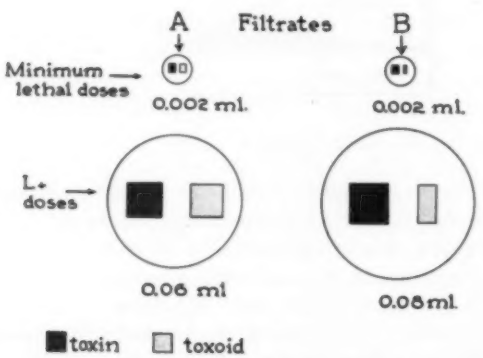

Chart 3.—The minimum lethal and L+ doses.

To clarify these relationships, let us postulate that we have two filtrates, A and B, from which we propose to prepare products for Schick tests. Suppose that one-half the toxin has changed to toxoid in A but only one-quarter of the toxin had been so converted in B (Chart 3). For simplicity let us suppose that they are equally toxic; 0.002 ml., for instance, of either A or B kills a guinea pig under standard conditions. So far as toxin is concerned, A and B are equal, but, in addition to toxin, A contains as much toxoid as toxin and B contains only one-half as much. Since antitoxin combines equally well with toxin and toxoid,

A contains more substance which will combine with antitoxin than does B. By reason of the greater removal of antitoxin by toxoid, less antitoxin will be available to combine with *toxin* in A than in B under otherwise comparable conditions. The only way to establish equal toxicity with the two filtrates, *after combining with a given volume of antitoxin*, will be to use more of filtrate B than of filtrate A. The L+ dose will be larger in B than in A, indicated in the example as 0.08 ml. of filtrate B and 0.06 ml. of filtrate A.

Traditionally, $\frac{1}{50}$ of the lethal or toxic dose of a filtrate is used for the Schick test.*[4] In these examples, this would be $\frac{1}{50}$ of 0.002 ml. of either filtrate. However, what we propose to measure in persons given the test, a threshold of antitoxin, fits exactly the concept of the L+ dose; that is, after combination with a threshold amount of antitoxin we desire a certain residual toxicity.

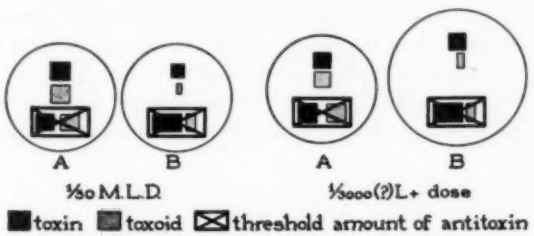

Chart 4.—Effects of the threshold amount of antitoxin on four Schick test products.

If we perform Schick tests with products made from filtrates A and B on a person who is a borderline reactor, with just the threshold amount of antitoxin, there will be a greater residual toxicity with A than with B. This will be apparent in the degree of inflammation, a delicate yardstick in this zone. The situation is indicated in the circles at the left in Chart 4. We have no means of knowing whether to rely on the Schick test made with A or with B. We may well falsely label the result as negative or positive, for A may produce inflammation and B may not on the same person. The concentration of antitoxin measured by the Schick test, based on what different performers with different lots of product have chosen to call barely positive tests, varies from $\frac{1}{20}$ to $\frac{1}{500}$ of a unit. The fact that the combining powers of filtrates are not standard in the products produced for Schick tests makes this undesirable variance inevitable.

After reaction with a threshold amount of antitoxin, we want an equal amount of toxin left in all cases. By using a fraction of an L+ dose instead of a fraction of a lethal dose for the Schick test, all products sold would be based on constant residual toxicity. Exactly what the fraction of an L+ dose should be would have to be determined epidemiologically. Precise data are not available because of the variation described. However, a first approximation cal-

*At least as far back as 1931 there was some recognition of the need for considering the combining power of toxin used for the Schick test. The test dose, mixed with 1/750 of a unit of antitoxin or more, should give a distinct negative test on an animal; and, with 1/1,250 of a unit or less, it should produce "a definite local reaction of the type known as the 'positive Schick reaction.'"

culated from averages of present and past lots, from existing data, would give a valid and useful figure. It would serve for the ten or more years that it would take to find the correct level for the Schick test, and would be a distinct improvement on the present situation.

Marked reactions in the Schick test probably mean susceptibility in nearly all cases. Likewise, many of the completely negative Schick reactions must also be beyond the range of error, though we do not know which ones are near the borderline. The Schick test is established as practically useful because the extremes are valid and the tendency is to play safe in cases of doubt. The mere fact that diphtheria occurs in negative reactors suggests, however, that some lots of Schick product may set the threshold of antitoxin in the wrong place. The use of a fraction of an L+ dose would improve the accuracy.

In addition to definite positive or negative reactions, in which some negative ones are suspect, there are many partial or borderline reactions. Under the present conditions, since borderline reactions cannot be said to have known significance, there can be only the usual answer, to designate all borderline reactions as positive empirically, for the sake of safety. Even though we cannot rely on borderline reactions, we should think twice about their possible immunologic meanings.

Under present circumstances two moves are still possible with doubtful reactors. First, if laboratory services provide the opportunity, Kellogg tests[5] can be performed. This test, based on the early Römer[6] units, has never been completely calibrated on the grounds of immunity, but it is a correctly constructed test. The serum of the blood of a person to be tested is mixed with a tested amount of toxin and is inoculated intradermally into a guinea pig. This transferred Schick test is based on a fraction of an L+ dose and is essentially a titration of antitoxin. Second, it is possible to test with several products, using carefully measured inoculations. Comparisons of reactions can reveal something about the range of activity and permit more accurate interpretations.

Ideally, a new standard might well be set for the Schick test, based upon the L+ dose instead of upon the lethal dose. The presence of varying proportions of toxoid cannot be ignored. The establishment of such a standard is a simple undertaking both technically and practically. Because it clarifies the borderline zone, its use is easier and offers no complications. Sociologically, it requires the coordination of the medical profession, producers of biologic products, and the legal controlling group in the National Institute of Health. Once a standard Schick test product is available, calibrated to a threshold level, not only should the Schick test be a more responsible test but the significance of borderline reactions would then have real meaning. The insecurity that accompanies interpretations of the many borderline reactions can and should be overcome.

SUMMARY

The Schick test should be so standardized that the scale of reactions between no inflammation and definite erythema should fall on either side of a definite threshold reaction, occurring in all persons with a threshold concentration of

antitoxin. Using the dosage of $\frac{1}{50}$ of a minimum lethal dose, even circumscribed by other standards, different lots of Schick test product cannot produce constant results in the many borderline reactors. Careful interpretation of borderline reactions is indicated, based on an understanding of the present status. The use of a fraction of the L+ dose of each toxin for the Schick test would be practically possible and preferable to the use of a fraction of the minimum lethal dose.

I am greatly indebted to Dr. Harry E. Foster for expert advice.

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RESERVOIRS OF INFECTION

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VIEWED by the biologist, an infection is analogous or identical to parasitism which exists throughout the entire animal and plant kingdoms. If the infective agent, the microbian parasite, is to survive and propagate, it must be transferred directly or indirectly from one living host to another—from the "dispensing" host to the "receiving" host. This exchange may be relatively simple, provided the microparasite is maintained by one species, or it may be intricately complex if the parasite is adapted to life in various hosts and reservoirs. It may be apparent in manifest clinical disease, or well hidden in concealed subclinical infection or inapparent in an arthropod.

According to a recently proposed definition, a reservoir is usually a living vertebrate, arthropod, or other creature in which the etiologic parasite survives, develops, or reproduces itself, and from which it can be transmitted to human beings. The possibility of reservoirs in animals must always be kept in mind, particularly if the microbian or viral agent can survive in many species—a variety of zoologically unrelated hosts—mammals, birds, and insects. Obviously, the highly specialized ecologic conditions necessary to support the biologic relationships which determine the incidence in human populations of microbian or virus diseases with multiple host relationships are complex.

Reservoirs of infection may be divided into two large groups: (a) Warm-blooded animals. The infection chain is homogeneous—the infection is maintained among a limited number of species. The parasite is likely to reach man by cutaneous, alimentary, or mucosal aerogenic routes. When animals serve as a reservoir of human disease, it must be recognized that the sporadic cases or outbreaks are, as a rule, extensions of prevailing enzooties in a state of renewed activity. (b) Arthropod vectors. This link in a complex animal-arthropod cycle of transmission may culminate in sporadic human infections.

Some parasites find it possible to live outside this cycle for some time. They are tough and resistant to physical insult. The influenza virus is known to survive in dust for up to two weeks[8] and smallpox virus can remain alive in dried-up crusts for over a year.[7] Rift Valley fever has been contracted in a room where infected mice had been housed three months previously.[10] The viral agent responsible for panleucopenia of cats persists in households for months and foot-and-mouth disease virus dried on hay or other material is readily transmitted. There is undoubted significance in the recent observations on poliomyelitis that the virus may be so overwhelmingly numerous in the feces of patients that it may be recovered from sewage and latrines in an epidemic area. Since the microparasite of poliomyelitis is capable of extra-

From the George Williams Hooper Foundation, University of California.

human survival, suggestive observations have, in recent years, incriminated sewage and manure as possible "reservoirs," potential routes for dissemination through food, drink, and fomites.[4, 15] The principal specific human endemic virus diseases are usually contracted rather directly by inhalation of droplets or air-borne droplet nuclei. However, another more devious mechanism may be equally important. Falling exhaled particles may adhere to clothing. Later, clouds of infective particles are liberated by shaking. These are unquestionable instances of survival of virus outside a living host. In general, however, inanimate nature is not considered to be a reservoir because it does not provide conditions favorable for continued survival of the virus. Chance may force the organism to live out its days outside a living host, but none show a preference for this independent existence.

If man is the sole spontaneous natural host, the principal reservoir, he bears the burden of providing the environment for continuous propagation of the parasite. To some, notably some of the viral agents, his existence is particularly essential because they are not well equipped to maintain themselves outside living cells. They must select simple direct routes between hosts in order to survive. The parasites of such infectious diseases as rubella, mumps, chickenpox, molluscum contagiosum, and warts are so dependent on the environment man provides that they can be transmitted only with difficulty or not at all to zoologically unrelated species. For such organisms there cannot be a large permanent reservoir outside the human host. On a priori grounds, this is evident for such organisms as meningococci, streptococci, pneumococci, *Hemophilus pertussis* and *H. influenzae, Corynebacterium diphtheriae,* and the enteric group, to mention only the more conspicuous examples.

When man becomes the host to an animal parasite, the transmission cycle as a rule is broken. Human infections are merely accidental aberrations in the infection chain. Man is not essential to this type of parasite. As a rule, human cases serve as sentinels, the visible indicators of an extra-human reservoir. Human-to-human infections are rare. Infections with bovine tubercle bacilli were formerly considered closed processes, conveyed only from animal to man, but in view of many observations in Scotland, man-to-man infection is now admitted. Rabies virus is present in the saliva of children and human-to-human transmission has been reported from Russia. Nurses, doctors, and visitors in contact with patients with advanced specific pneumonia have acquired psittacosis and ornithosis. The recently reported true epidemics of pneumonitis due to psittacosis-like agents provide a clue to the process by which animal disease of ancient lineage may give rise to new human infection and likewise emphasize the importance of man-to-man transmission of animal viruses. Recently Q fever was apparently acquired by a nurse and two attendants of a patient with severe pneumonia.[5]

The clinical and anatomical character of the human disease created by a mammalian or avian microorganism, protozoan, or virus, is frequently similar to that in the animals. A change in host apparently does not alter the principal diagnostic signs provided the portal of entry of the parasite is the same.

The usual sequence of discovery of the chains is from human to extrahuman infections, but this sequence may be reversed: a "new" human disease may be identified after the animal reservoir is discovered. In equine encephalomyelitis, for instance, human infections were recognized in 1932 shortly after the nature of the horse disease became apparent and the virus was isolated from human tissues in 1937. For over a century, louping ill has been known to exist among sheep in Scotland and North England. Until recently there was no reason to believe that human beings acquired this disease under natural conditions. The records of twelve laboratory infections in the United States, Great Britain, and Germany did not attract attention until it was demonstrated that the pantropic viral agent of Russian spring and summer (Far Eastern), tick-borne encephalitis is antigenically closely related to the louping-ill virus of sheep.[9] Under the impact of this knowledge, it is not surprising that at least four human louping-ill infections occurring naturally were diagnosed in Scotland.[2, 3, 14] The clinical picture is that of meningoencephalitis preceded by an influenza-like infection. The rapid multiplication of the virus in the primary phase assures its circulation in the blood. It later disappears from the blood, but appears in the central nervous system and spinal fluid, and symptoms of encephalitis develop. In human infections it can be readily isolated from the spinal fluid. It is not unlikely that many human infections have occurred in Scotland, but terminated after the first phase, and the diagnostically significant symptoms of encephalitis did not develop. Serologic surveys in a slaughterhouse in Scotland brought to light at least three, possibly six unrecognized infections in a group of thirty-eight employees. Contact transmission by infected material through skin abrasions or by the bite of infected ticks is suspected.[14]

When an animal is identified as a reservoir of disease, it becomes imperative to know something about the means of spread and the species of animal that is the victim. Only in the field of ornithosis is knowledge sufficiently detailed or significant to warrant generalizations.

Many microbian and viral agents living in animal hosts exhibit an outstanding tendency to cause chronic, latent, or subclinical infection, and the part played by human carriers as permanent sources of infection has gained recognition ever since Koch[13] interpreted the observation on diphtheria by Escherich and on cholera that conspicuous infections are not the sole source of contagious diseases. The dog, cat, and barnyard fowl occasionally transmitting Salmonella diarrheal disease to children, as a rule, appear perfectly well. Without arousing suspicion and without the owner's even realizing that they had been ill, dogs may excrete leptospira and may serve as dangerous sources of infection for entire families. Milk and dairy products derived from "healthy" cows and goats may carry Brucella or the Q fever organism.

Dogs infected with *Taenia granulosa* rarely show any signs indicative of intestinal infestation, but pollute continuously their environment with the eggs which accidentally may gain access to children's mouths. In ornithosis and psittacosis, the apparently healthy birds, and in lymphocytic choriomeningitis of mice, the convalescent and chronic carriers continuously or intermittently shed

virus in their fecal droppings or in the urine and thus create the problem of the hidden reservoir. The saliva of blood-lapping vampire bats (*Desmodus rotundus murinus*) of Trinidad may be found infective, although they show no obvious manifestation of disease. The death of a laboratory worker and, in all probability, of a King of Greece, both after being bitten by apparently normal monkeys, led to the isolation of virus B. In the course of detailed studies by many workers it was recognized that this virus, apparently similar to the herpes virus, lives in symbiosis in the monkey, but when transmitted to man it may cause a fatal infection.

Any discussion of reservoirs must include attention to the ever-increasing vector significance of the poikilothermic, biting arthropods. Their role in the transmission of filariasis, piroplasmosis, malaria, trypanosomiasis, relapsing fever, plague, and the large group of rickettsial infections is well known. In recent years the discovery of virus reservoirs in arthropods has enlarged the horizon of epidemiologists. Proof of the role of arthropods as vectors has been fully established (1) by the isolation of the virus from pools of naturally infected insects, (2) by artificial transmission of the infection, and (3) by isolation of the virus from arthropods fed on patients. The naturally infected insects, as a rule, are trapped in the vicinity of patients during outbreaks. For transmission, the arthropods suspected as vectors are permitted either to bite infected patients or to feed on virus preparations. They are then transported to places where the disease does not occur naturally and allowed to bite volunteers who may become infected. Finally, newly hatched arthropods may be fed on infected human beings and the presence of the virus in the vector may be proved by inoculation or feeding tests.

Arthropods can become infected by man only if they suck blood while the agent circulates in the peripheral blood (viremia); this period of potential infectivity may extend from a day before the onset of symptoms to three to five days thereafter. After feeding, several days may elapse before the vector can infect other persons. This period of "intrinsic incubation" is necessary to allow the virus to reach the salivary glands in concentration. Once infected, arthropods harbor the virus for the rest of their lives, usually not beyond the end of a single season.

In classical urban yellow fever and dengue fever, the arthropod vector serves as a temporary seasonal reservoir. Since the virus apparently does not survive the arthropod vector, the mode of persistence and perpetuation of the infection from one season to another remains obscure. There is little evidence that yellow fever or dengue virus multiplies in the body of the mosquitoes, though the incubation time is usually prolonged in cold weather. In the ecology of sandfly fever, it seems likely that the virus must survive in the insect carrier, *Phlebotomus papatasii*, because human cases have not been sporadic nor have animal reservoirs been proved.

During the past decade it has become increasingly evident that in several arthropod-borne diseases, man is not the only source of infection and that in some arthropods, hereditary transovarian passage provides the means of survival for the virus. The survival of viruses in the Ixodes tick population re-

sponsible for Russian Far Eastern encephalitis and for louping ill is attributed to proved transovarian transmission. Ticks apparently serve as a true constant reservoir and hence the period of infectivity, viremia, lasts only a short time in the numerous hosts. The virus of Colorado tick fever, clinically similar to dengue fever, is preserved in the transmitting tick *Dermacentor andersoni* through transovarian passage to the next generation. It is significant that tick viruses in the intermediate vertebrate hosts live and multiply without producing any pathologic effect. Biologic adaptation here approaches perfection.

With the recognition of jungle or sylvan yellow fever, commonly contracted by woodcutters and road constructors working in the rainy forest belts of Colombia and Surinam or the shrubby grasslands in Brazil, a new type of reservoir for virus infections has been discovered. It has now been proved that this form of yellow fever is primarily a disease of forest vertebrates. In the marmosets and other monkeys, viremia develops when they become infected with the virus and the infective agent circulates in their blood for seven or eight days. When it is picked up by the mosquitoes (*Haemagogus capricorni*), it remains with them for the duration of their lives. Moreover, recent investigations[1] have demonstrated that at suitable temperatures, virus multiplies progressively in the mosquitoes. Though this vector appears to be a permanent reservoir of the yellow fever virus, it is reasonable to suspect that alternate cyclical passage through insects and vertebrates without extension to man maintains the complex hidden reservoir in the canopy of the jungle forest. There is some evidence that subclinical infections are not infrequent in people living in jungle areas of South America. Recent accounts[16] suggest that hitherto unrecognized yellow fever may be prevalent in the uninhabited Semliki Forest of Uganda and the Langata Forest of Kenya. Certain lower primates and other wild arboreal species of vertebrates together with jungle mosquitoes *(Aedes africanus)* may constitute the reservoir of African sylvan yellow fever.[16]

A number of viruses have been isolated from pools of mosquitoes caught in areas where yellow fever is being studied. At present they are of interest merely because they are probably present in wild animals and are transmitted by mosquitoes. Rift Valley fever, also known as enzootic hepatitis, among sheep flocks, occasionally transmitted to sheep herders in Kenya Colony, presumably has a reservoir in wild animals and a vector in mosquitoes of the Aedes group. The position of the vertebrates and arthropod host as a reservoir is obscure.

New and intriguing problems confront the ecologist interested in the mosquito-borne encephalitides (St. Louis, Japanese, and equine encephalomyelitis) causing disease both in man and in animals (horses). The spread of these virus infections has a great deal in common with that of yellow fever, but avian hosts enter the inapparent transmission cycle. For instance, mosquitoes have been found naturally infected in endemic areas; probably *Culex tarsalis* is the main vector. The source of virus in nature appears to be the blood of small wild birds and, to a minor extent, of pheasants, pigeons, and prairie chickens. Horses and man are infected only accidentally and do not play an integral part in the life cycle of the virus. Still unanswered remains the question of which of the

two components in the transmission cycle is the reservoir and of how the virus survives the winter. In at least one disease, St. Louis encephalitis, evidence indicates that the true reservoir may be tiny bird mites (Dermanyssus and Liponyssus) which do not bite any mammals. The virus may be passed through the egg to the progeny without the necessity of an intermediate vertebrate host. None of the hosts in the natural cycle—mite-bird-mosquito—become ill, but when infected mosquitoes bite a mammal or a human being, a severe and possibly fatal disease may occur. Many of the observations reported have been made on the Pacific Coast. It is reasonable to suspect that the ecology of the encephalitides on the Atlantic Coast and in the Central States may be different and the reservoirs even more complex.

Finally, the possibility that rats and cotton rats may participate in creating a reservoir for another group of viruses has recently been suggested. In recent years it has been proved[6, 13] that the so-called Mengo encephalomyelitis virus isolated from a human patient, from a pyrexial Rhesus monkey, and from a batch of Taeniorhynchus mosquitoes is identical with the encephalomyocarditis virus of Warren, Smadel, and Russ,[18] the Colombia SK originally isolated by Jungeblut and Sanders[11] from cotton rats infected with a poliomyelitis virus, and the MM virus of Jungeblut and Dalldorf.[12] Now it has been established that 87 per cent of wild rats collected in Missouri possessed specific neutralizing antibodies.[17] If further studies substantiate these observations, it will be most intriguing to elucidate the ecology of the suspected mosquito-rat transmission cycle and to determine the reservoir function of the vertebrate or the arthropod.

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THE OBSTETRICAL SIGNIFICANCE OF PREMATURITY

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ACCORDING to the studies of numerous investigators, prematurity is the most prominent cause of stillbirth and neonatal death. While there has been reduction in the death rate over the years—and especially since 1940—in both premature and term fetal mortality, the improvement has been by no means as spectacular as the improvement in maternal mortality over the same period of time (Chart 1).[1] The bulk of the recent improvement which has occurred in the premature infant mortality rate has been in the care of the infants *after* birth, and even after the neonatal period. Comparatively little of it has been due to better obstetrical management (Chart 2).[2] In Tyson's[3] series, there were 1,140 premature deaths of which 522 were stillbirths and 618 occurred neonatally, 81 per cent within the first forty-eight hours. In Potter's[4] series, 74 per cent of neonatal deaths occurred within the first twenty-four hours. These early deaths, which greatly outnumbered those occurring later, were largely attributable to complications of pregnancy, labor, and delivery. In short, they were the obstetrician's responsibility in the sense that they could not be attributed to the lack of proper pediatric care. Thus prematurity remains one of the major unsolved problems of obstetrics, and to a lesser extent, of pediatrics.

The premature infant is more likely to succumb than the term infant, because, in simplest terms, it is not ready for extrauterine existence. Its metabolic processes, defense mechanisms, and many of its organs have not yet developed sufficiently to cope with the atmospheric, climatic, and nutritional conditions of this world. More specifically, pulmonary complications rank high as causes of death—asphyxia, atelectasis, and pneumonia have accounted for a large proportion of premature mortality. Congenital defects incompatible with life have been common. Intracranial hemorrhage has been found also though one cannot always be certain whether it was asphyxial or traumatic.

It is common practice among obstetricians to define prematurity as weight between 1,500 and 2,500 grams, or length between 35 and 45 cm., and most of the figures dealing with incidence are based upon this standard. Babies weighing less than 1,500 grams have been regarded as having little chance for life or actually nonviable. Whatever the original basis for such an artificial division, this practice is certainly no longer valid for a goodly number of babies weighing less than 1,500 grams, and even a few weighing less than 1,000 grams, will survive. Therefore these very small babies must definitely remain a part of the problem. At what point in the fetal size we should switch from the designation *abortion* to *premature birth* is a matter of academic interest only, at least when we are dealing with a liveborn fetus.

Of tremendous importance, however, is the correlation between survival and size. All observers are agreed that the chance for survival is directly related to

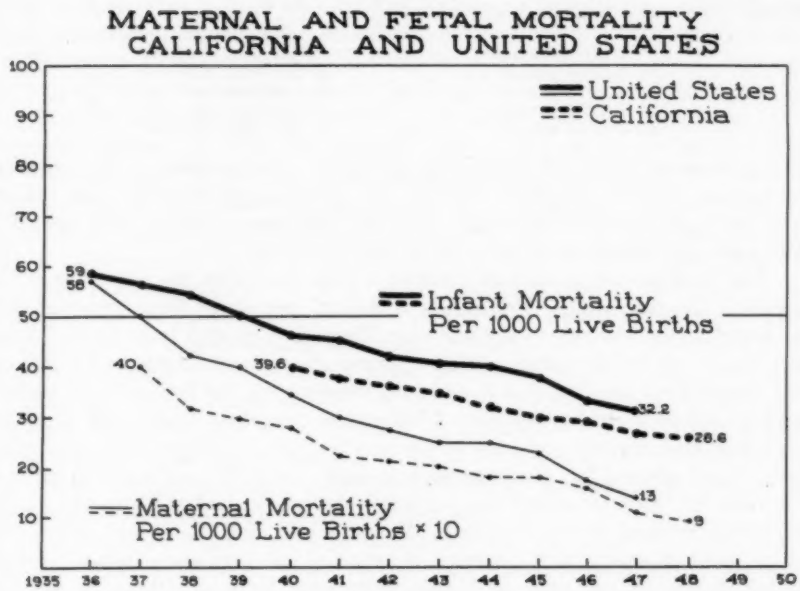

Chart 1.

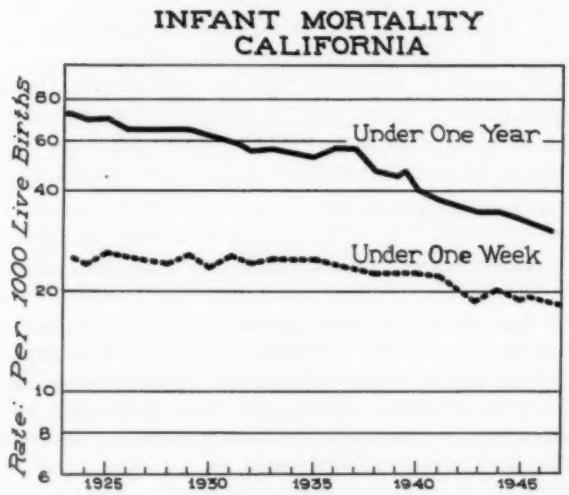

Chart 2.

the size of the infant. From his study of 2,960 premature births, Tyson[3] (Philadelphia, 1946) obtained the following table:

---1,000 grams	2 per cent survival
1,000-1,364 grams	20 per cent survival
1,364-1,818 grams	46 per cent survival
1,818-2,272 grams	81 per cent survival
2,272-2,500 grams	91 per cent survival

Similar observations have been made by many other authors. The practical implication is quite apparent; namely, the most important thing that the obstetrician can do is to delay labor until the fetus has attained a safe size, if it can be done without jeopardizing the life of the mother.

The incidence of prematurity varies a good deal with the character of the material. At the New York Hospital it was 2.7 per cent;[5] Dana reported 2.95 per cent;[6] at the University of California Hospital it ranged from 5.9 to 7.3 per cent during the last five years. Higher figures are those of Tyson[3] and Eastman[7] who reported 9.4 per cent and 11 per cent, respectively, but both of these authors included babies weighing less than 1,500 grams. In these studies the incidence has not varied greatly with age of the mother, nor with race, but some other factors have affected it. Eastman gave an incidence of 7.8 per cent among those who received "good antenatal care (at least three visits) and 24.9 per cent among those who received poor or no care. Brown, Lyon, and Anderson[8] found that 5.5 per cent of women with "normal" pregnancy had premature babies, whereas approximately 13 per cent of women with some form of illness did so. In Tyson's[3] series, in 750 cases in which the mothers received a diet high in protein, minerals, and vitamins, there were no premature births, whereas among an equal number on unregulated diets there were 37 premature births. These figures suggest at least that the provision of good care and adequate diets to all patients might result in a reduction in the incidence of prematurity.

Many of the causes of premature birth are well known, though no one of them can be regarded as a major cause, i.e., major in the sense of causing a significantly large number of premature births. The following incidences were compiled by Brown, Lyon, and Anderson[9, 10, 11] in their several publications:

Among syphilitic women	15.5 per cent
Among those with toxemia	11.0 per cent
Among those with slight bleeding	14.0 per cent
Among those with placenta previa	30.0 per cent
With abruptio placentae	53.0 per cent

But not one of these complications of pregnancy is very frequent.

Other maternal diseases also contribute in a small way, such as nephritis, pneumonia, anemia, and leucemia. Prematurity is also associated with certain conditions related to the fetus and placenta, such as placenta previa and premature separation of the normally implanted placenta, multiple pregnancy, hydramnios, fetal anomalies, erythroblastosis, etc.

Most baffling of all, and most important of all, a *large proportion* of premature births occurs *without* apparent cause. There is *no* demonstrable disease, and no abnormality. Eastman[7] was unable to assign a definite cause in approximately 60 per cent of the premature births in his series. Dawson[12] of New Zealand attributed 17 per cent of all infant deaths to unexplained prematurity.

In attempting to account for "unexplained prematurity," malnutrition was given a large place by both Stander and Eastman. Deficiencies in protein, mineral, and vitamin intake were considered particularly important by both men. In Eastman's series of over 3,000, the incidence of prematurity among those who had "good care" (which we assume means good nutrition also) was only one-third of that among those who received poor care. This is an extremely important idea because, if valid, one method of improving results among premature infants lies clearly before us. Yet I do not feel that this particular thesis has been proved beyond peradventure because all of us in our private practices, wherein nutrition is almost surely adequate, have had a not inconsiderable number of patients who have gone into labor prematurely without explanation.

One can only speculate about other possible causes of unexplained premature birth. Psychological factors are undoubtedly responsible once in a while. Trauma and fatigue must also take their occasional toll. Deviations from the normal of certain of the hormone levels are known to precede the premature termination of pregnancy. Lyon,[13] of our department, showed that the pregnanediol level dropped before abortion and premature labor. The Shutes[14] maintain that an excess of estrogen in the blood presages early termination of pregnancy. Whether these or other hormone changes are causally related to the occurrence of prematurity remains to be settled.

One wonders if there could be an interference with the mechanism of "conversion" recently described by Reynolds,[15] as a change in the shape of the uterus from globular to ovoid at about the seventh month, signifying the beginning of the fetal maturing period. This is an unexplored field. Since premature rupture of the membranes precedes or ushers in the onset of premature labor, some tie-up with the mechanism of conversion might well exist. Knox and Hoerner[16] have suggested that premature rupture of the membranes is often associated with *infection* of the dependent portion of the sac, and that such infections may therefore cause weakening and rupture. This too requires further consideration.

This is the background then; the frequency, the causes, and the consequences of prematurity have been related. What can the practicing physician do about it? In our present state of knowledge we cannot solve the problem, but there is a good deal to be accomplished by careful attention to certain precautions. These will be discussed in some detail.

It goes without saying that most of the precautions are entirely dependent upon early and adequate "antenatal care."

1. Detect early and correct maternal disease. I need not dilate upon this particular phase of the subject. Ordinarily, maternity patients have histories taken and examinations made at an early period in pregnancy and naturally an effort is made to combat whatever pathological conditions exist. For example, if it is syphilis, proper treatment is provided; if it is anemia, iron is prescribed or transfusion is performed if necessary. With regard to the development of disease during the course of pregnancy, reasonable efforts are made to treat patients as early and as thoroughly as possible. Antenatal care with its periodic checkup examinations is directed particularly toward the avoidance of toxemia. In spite of this, it *does* occasionally develop and, as indicated above, it *is* associated with premature labor in a significant number of the cases. At least the

medical profession is thoroughly aware of this problem and makes elaborate efforts to solve it.

2. Provision for proper nutrition. Ordinarily dietary advice is given at an early period in the pregnancy. Good nutrition in pregnancy seems to depend upon an adequate supply of protein, minerals, and vitamins particularly, and some limitation in sodium chloride and calories. Ordinarily a well-rounded diet contains these items, but supplements are often added as a matter of precaution. Those who do not carry out the advice fail to do so because of indifference or because they are financially unable to buy the necessary foods. Probably nutritional needs, insofar as we know them, are adequately supplied in the case of the vast maority of private patients in this country. Certain clinic populations may be deficient for economic reasons.

3. The conservative treatment of bleeding in the third trimester of pregnancy. Placenta previa and premature separation of the normally implanted placenta together are responsible for a sizable block of the cases of premature labor. So far as we know there is no measure which can be taken to avoid placenta previa. Probably the same is true of abruptio placentae, though it is said that the incidence of the latter is less where nutrition is good, and possibly also it is influenced by certain hormonal conditions according to the Smiths. We know, too, that a few of the more severe cases of premature separation of the placenta are associated with toxemia, and thus the avoidance of the latter may contribute to the avoidance of the former. Be this as it may, many patients who have started to bleed before the period of viability can be carried to a time when the baby is big enough to survive if the effort is made to do so. Hospitalization and bed rest, and possibly stilbestrol, may result in the cessation of bleeding and the deferment of labor for prolonged periods of time. Such a regimen is indicated whenever the baby is of questionably viable size, unless hemorrhage is persistent or recurrent in dangerous amounts. In the latter event immediate delivery becomes imperative. It is often possible, in this way, to tide the patient over, until her child reaches a viable size.

4. Spontaneous premature rupture of the membranes, or the onset of labor without rupture of membranes for unknown reasons. These cases of unexplained prematurity occur more commonly than those for specific reasons as previously indicated, and thus this is a very important group. There is, of course, no certain way to avoid delivery if labor sets in or the membranes rupture prematurely. However, on occasion, a patient may *not* go into labor for days, weeks, or even a month or more after rupture of the membranes. Some have regarded such patients as likely candidates for intrauterine infection and have therefore advised early efforts to stimulate labor. Others, and that includes myself, believe that the danger of infection is slight, and advise making every effort to discourage the onset of labor if the child is of such small size as to jeopardize its survival. Possibly if some cervical dilatation has occurred, the danger of infection is greater. The question of the use of antibiotics prophylactically in such cases arises. It might be advisable, though we have no definite information one way or the other at this time.

What measures can be taken to discourage labor? Estrogens, particularly stilbestrol, in large doses, are being widely used for this purpose. The results

are not clear-cut, but it is my impression that most observers believe that it is successful at least in part. Since no harmful effects have been demonstrated, I can see no objection to trying it. Stilbestrol in doses ranging from 15 to 100 mg. a day is common. Rest in bed has been recommended traditionally and is probably of value. According to Shute, but to hardly anyone else, vitamin E is valuable in this respect. In 63 cases of threatened premature labor, "73 per cent were salvaged" by vitamin E and bed rest. Shute advises 75 to 125 mg. alpha-tocopherol daily.

5. Conduct of labor. If in spite of our efforts to the contrary, premature labor does indeed supervene, what may be done in the conduct of the labor to reduce to a minimum the hazards to the baby? All are agreed that one of the most important considerations is maternal sedation. Premature babies seem to be excessively susceptible to the effects of sedative drugs administered to the mother in labor. All obstetricians are aware that asphyxia and atelectasis account for a great deal of premature fetal mortality. Practically all of the sedative and analgesic drugs employed in labor depress the fetal respiratory center, thus favoring the development of the unwanted conditions mentioned before. It behooves us then to keep sedative and analgesic medication to the barest minimum in such cases. Oxygen administration should be considered whenever the fetal heart varies from a safe average, either during the course of labor or the actual delivery. Local and regional forms of anesthesia are advised by Eastman, Dippel, Johnson and Cornelison, Labate, and many others. It seems clear that one of the biggest contributions the obstetrician can make is to avoid analgesia and anesthesia which may lead to fatal anoxia. Pursuance of this policy at the University of California Hospital has undoubtedly contributed heavily to the phenomenally low premature fetal mortality rate achieved at this hospital during the last five years.

If the membranes have not ruptured, every effort should be made to keep them intact, since the forewaters act as protection for the fetal head. The term baby does not seem to require this protection; the premature baby may. Strong expulsive efforts should be avoided, as should pressure on the uterine fundus. When the head reaches the perineum an ample episiotomy should be performed. All of these measures tend to the avoidance of undue stress on the not yet mature fetal cranium, and thus may assist in circumventing tentorial tears and the like. The actual method of delivery, i.e., whether spontaneous or instrumental, does not seem to be of great importance according to Drillien[17] and also to Tyson, except in the case of breech presentations, in which case the fetal mortality among premature infants is excessively high. The method of delivery in vertex presentations is of some interest since many obstetricians speak of forceps deliveries as "prophylactic"—as if lifting a baby's head out of the pelvis by this means were less traumatic than allowing it to come naturally. As long as progress is normal and there is no undue prolongation of the perineal stage, the wisdom of the policy of routine forceps delivery is open to question.

As soon as the baby is born, prompt and careful attention must be given to the matter of establishing respiration. Ample oxygen should be supplied, and every effort should be made to prevent a marked and prolonged drop in

the infant's temperature though some initial drop may be advantageous as an aid in establishing respiration. Sometimes body temperature is sadly neglected while other procedures are being carried out. This should be avoided. Many observers advise not clamping the cord immediately with the idea that such a course may deprive the baby of a significant amount of blood. The notion of conserving blood is undoubtedly a good one. McCausland's[18] recent work would seem to indicate that a better, quicker, and surer way to accomplish this might be to milk the blood in the cord toward the infant several times and then clamp.

By way of avoiding in the newborn infant a bleeding tendency on the one hand, and infection, particularly pulmonary infection, on the other, several authorities advise the administration of vitamin K and penicillin during the course of labor. Neither of these measures has been completely proved, however.

It is at this point that the obstetrician needs the cooperation of the pediatrician. Expert attention in the nursery often means the difference between life and death. Only the obstetrical side of the story has been told. The care of the baby during the first very critical forty-eight hours, when approximately 70 per cent of the premature deaths occur, belongs to the pediatrician. It is plain to see that the best results can be achieved only through close cooperation between obstetrician and pediatrician. If we believe that life is valuable, and I believe that we do, this endeavor to cut down the incidence of prematurity, and to deal most efficiently with premature labor when it is forced upon us, and to provide the best care for the premature baby when it has finally arrived, is very well worth while. It has been shown that, barring central nervous system injury of permanent nature, once the premature becomes mature, it makes a no-less-sturdy child and adult than does the full-term infant.

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COARCTATION OF THE AORTA IN CHILDREN

Observations in Fourteen Cases

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THIS paper embodies the observations in fourteen case of coarctation of the aorta, twelve of which were in males and two in females. The ages ranged from 4½ months to 14 years. In seven of these patients, the ages varied from 10 to 15 years, and in the other seven patients, the ages varied from 4½ months to 6½ years. Twelve of the fourteen patients had surgical repair of the coarctation. These patients have been observed from the first operation in May, 1947, to the last operation in January, 1950.

It is of extreme interest that five of the youngest patients in this group (Group I), with ages ranging from 4½ months to 4½ years, were hospitalized because of cardiac decompensation. The presenting symptoms in this group of five, and in their order of frequency, were as follows: dyspnea was present in all of the five patients, marked head sweating was present in three, and edema of the face and lower extremities in one.

On physical examination, the following salient features were noted: A precordial bulge, consisting of a forward projection of the manubrium and body of the sternum, and marked cardiac enlargement to the right and left of the sternum were present in the entire group of five. A systolic murmur to the left of the sternum, usually most intense in the third interspace, but occasionally transmitted all along the left sternal border, was present in four of the five patients. Hypertension in the upper extremities and weakly palpable or absent femoral pulses were found to be present in the entire group of fourteen patients. It is possible with a small cuff to make reliable blood pressure determinations on infants. Poor development, demonstrated by spindly legs, poor tissue turgor, and pallor inconsistent with the hematological picture, were present in the five younger patients.

The x-ray examination of the heart (Figs. 1 and 2) in these cases showed generalized cardiac enlargement and the aortic knob was poorly visualized. None of these patients (4½ months to 4½ years) showed notching of the ribs.

The electrocardiogram (which in coarctation of the aorta would be expected to show left ventricular hypertrophy) showed right ventricular hypertrophy in three cases; no clear evidence of right or left ventricular hypertrophy in one case; and none was obtained in the youngest patient.

Retrograde carotid arteriograms were done in four of the five patients in this group. Coarctation was well demonstrated in all of them. The usual site

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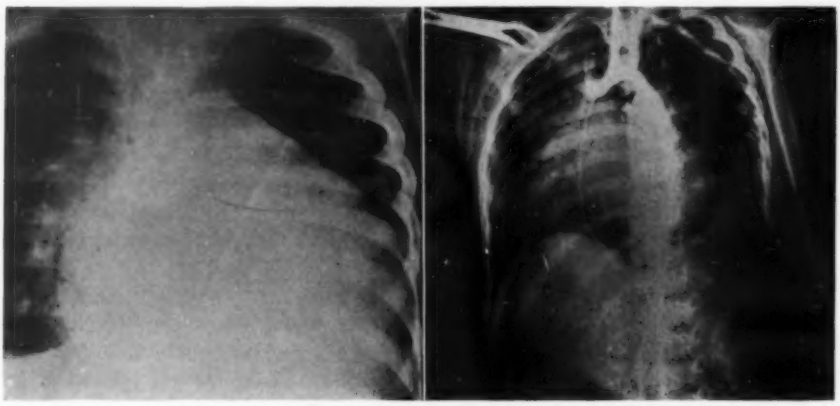
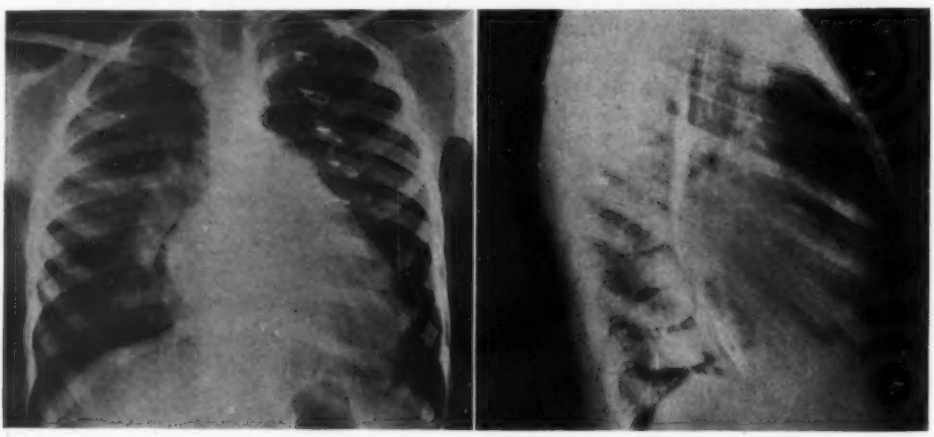
was just distal to the ligamentum arteriosum. It is significant that there is no evidence in the Diodrast cardiograms of the presence of appreciable collateral circulation (Fig. 3). This may be of extreme importance in view of the fact that other children in this same age group with presence of coaretation and the absence of decompensation or without significant cardiac enlargement show a high degree of collateral circulation even at an early age. In four of the five



A. *B.*

Fig. 1.—D. B., aged 4½ years. *A*, Anteroposterior roentgenogram of the chest. Note tremendous size of the heart and the congestion of the lung fields. *B*, Oblique view retrograde arteriogram. Note the lack of collateral circulation and the hypoplastic aortic arch. The arrow points to the site of coarctation.



A. *B.*

Fig. 2.—D. B., aged 7½ years. *A*, Anteroposterior roentgenogram of the chest. Three years after resection of the coarctation and end-to-end union. Note the satisfactory decrease in the heart size. (Compare with Fig. 1.) *B*, Lateral roentgenogram to show anteroposterior diameter of the heart.

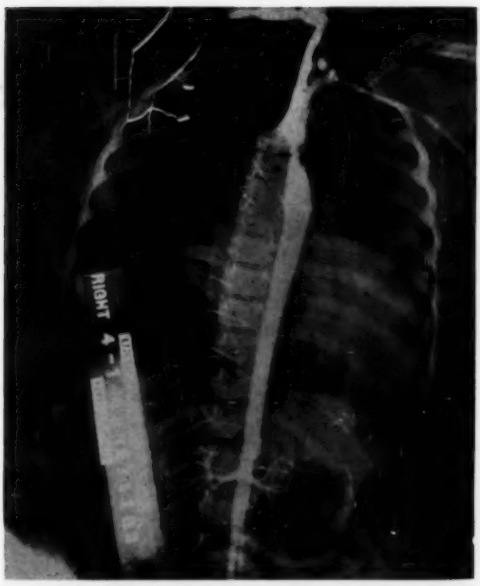
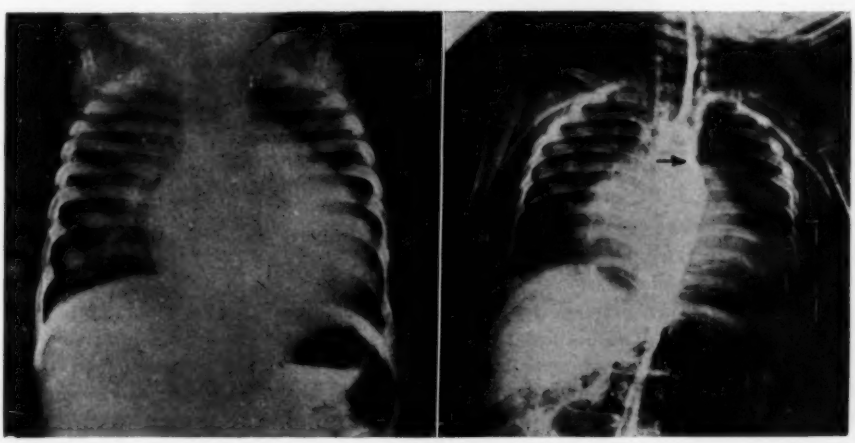


Fig. 3.—D. J., aged 2 years. Retrograde arteriogram. Arrow points to site of coarctation. Note the absence of collateral circulation.



A. *B.*

Fig. 4.—R. M., aged 14 months. *A*, Note marked cardiac enlargement (necropsy revealed no other lesions than hypoplastic arch and coarctation of aorta). *B*, Retrograde arteriogram. The arrow points to the site of coarctation. Note the absence of collateral vessels and the hypoplasia of the entire proximal aortic arch.

cases there was definite hypoplasia of the aortic arch (Fig. 4). We are of the belief that this may be a significant factor in the causation of the cardiac failure these patients manifested. Associated mitral valve stenosis was demonstrated in two of the five cases (necropsy findings).

The presenting symptoms in the nine patients (Group II) who were not hospitalized because of decompensation were related to claudication in the lower extremities produced by exercise in all nine patients: flushing of the face in four patients, acute episodes of exertional dyspnea in three patients, and headache and excessive fatigue in two patients.

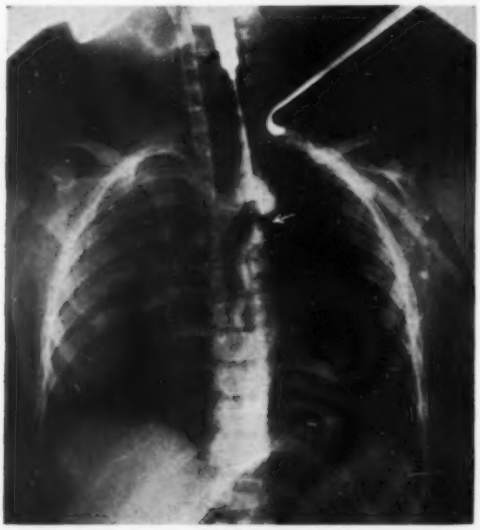


Fig. 5.—R. H., aged 6½ years. Retrograde arteriogram. The arrow points to the site of coarctation. Note the marked enlargement and tortuosity of the left internal mammary artery.

The physical findings in these patients were not remarkable except for hypertension in the upper extremities. The hypertension varied little between the arms except in one patient in whom the right subclavian took off below the coarctation in which instance the left arm pressure was 140/88 and the right arm 73 by palpation. The highest pressure at rest was 185/90 (RAR) in a boy 14 years of age. The youngest child in the group had a pressure of 160/100 in his right arm and 155/90 in his left arm. A single systolic murmur was present in eight patients heard best in the second or third interspace to the left of the sternum, transmitted into the neck and down the spine. Strikingly good physical development was noted in four patients, coldness of the lower extremities in three patients, cardiac enlargement in three patients, and suprasternal pulsation in one patient.

The x-ray examination of the heart in Group II confirmed the three cases with cardiac enlargement and demostrated either small or absent aortic knob in

five cases. There was demonstrated notching of the ribs in four cases. The youngest patient showing notching was 6½ years old.

In the retrograde carotid arteriograms in this group of cases, hypoplasia of the proximal segment was demonstrated in three, and distal hypoplasia in one. A well-developed collateral circulation appeared in seven patients (Fig. 5), moderately well-developed in one, and in another patient the roentgen films were not available for study. The coarctation usually was located just distal to the ligamentum arteriosum except in one patient (Fig. 6) in whom it was shown to involve the aorta from the level of the 11th dorsal vertebra to the 1st lumbar vertebra. The upper thoracic aorta was normal in appearance in this patient. Had it not been for the retrograde arteriogram in this patient, it would have been impossible to locate the true site or to determine the extent of the coarctation.

Fig. 6.—F. G., aged 14 years. Retrograde arteriogram. The arrows point to the site of coarctation. Note the marked collateral circulation and the normal proximal aorta.

The electrocardiogram was within normal limits in four of these nine patients and showed left ventricular hypertrophy in the other five patients. It is worthy of note that with decompensation there is right ventricular hypertrophy as has been previously mentioned.

PATHOLOGICAL FINDINGS

The pathological findings were determined by operation and/or necropsy in thirteen of the fourteen patients. The patient with coarctation of the lower thoracic aorta had numerous other congenital defects, and although there was

marked hypertension in the upper extremities (244/130 RAR and 228/125 LAR) a graft replacement of this defect, although technically possible, was considered ill-advised.

Fig. 7*A*.—J. M., aged 13 years. Proximal segment of the aorta demonstrating a pinpoint opening at the site of coarctation.

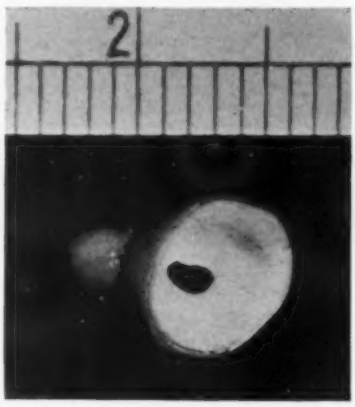


Fig. 7*B*.—R. M., aged 14 months. Operative specimen from Fig. 4.

The area of coarctation was just distal to the left subclavian take-off in all the other patients. The extent of stenosis within the lumen could not be determined accurately from the external appearance of the area of coarctation. The opening at the site of coaretation (Figs. 7*A* and *B*) usually was 1 to 2 mm. in

diameter. In one patient, there was complete obliteration of the lumen with no pulsation in the distal segment. The longest coarctation measured 2 cm. Again attention is called to the value of the retrograde arteriogram in this respect since possible need of a graft at the time of operative repair can be determined from this examination. Vegetations were demonstrated in the segment of the aorta just distal to the coarctation in one patient and at the site of coarctation in another. There had been no symptoms of embolic phenomena in either of these two patients. It was necessary to excise an additional 1½ cm. of the lower aortic segment in the patient where the vegetations were present in the distal segment. Atheromatous changes were present at the site of coarctation in two patients aged 13 and 10¾ years.

Subacute bacterial endocarditis was a proved cause of death in one patient and a probable cause of death in another and will be further discussed in the paragraph on the selection of patients for operation.

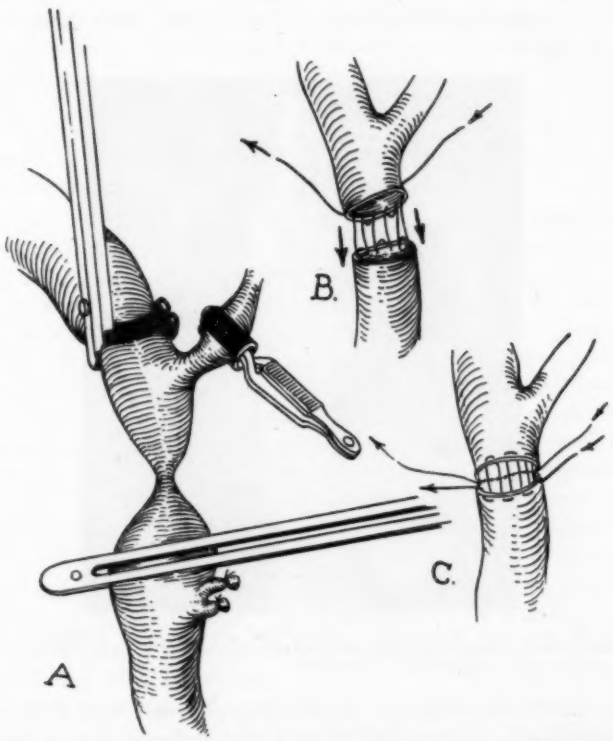


Fig. 8.—D. B., aged 4½ years. Steps in operation for coarctation of the aorta demonstrated in Fig. 1. *A* shows the manner of controlling the aortic segments. *B* shows the coarctation excised and the posterior layer of the continuous everting mattress suture inserted. *C* shows the posterior layer brought home; the anterior layer has been set and is now ready for tightening.

SURGICAL ASPECTS

Surgical correction of the coaretation was carried out in twelve patients. Resection of the coaretation with end-to-end anastomosis (Fig. 8*A*, *B*, and *C*) was accomplished in three of the five patients in Group I and in five of the nine patients in Group II. Following excision of the coaretation, when end-to-end closure was possible, a running posterior everting mattress suture was inserted, anchored at either end, and the same type of suture was used to close the anterior layer. Deknatel 00000 oiled silk was used routinely. In one patient having an end-to-end anastomosis following resection of the coaretation, longitudinal incisions were made in both segments to increase the lumen. The left subclavian artery was used to span the defect by end-to-end suture to the distal aorta in one patient in Group I and in one patient in Group II. A plastic repair of the aorta at the site of coaretation was carried out in one patient; the mesial wall was left intact, excising the remainder of the coaretation, then the lateral wall was reconstructed by uniting the proximal subclavian artery and the distal aorta. A very satisfactory lumen was obtained. The Blalock-Park operation (Fig. 9) (end-to-side, subclavian to distal aorta) was carried out in one patient in Group II.

Fig. 9.—R. H., aged 8½ years. Retrograde arteriogram. Approximately two years after the Blalock-Park operation. Note the excellent function of this anastomosis. Compare with Fig. 5 to see the preoperative arteriogram.

The length of time required for the surgical repair varied from 8¾ to 4¼ hours. Anesthesia in the majority of cases was produced with nitrous oxide and oxygen and Pentothal. Curare was used intravenously to obtain muscle relaxation. Fluid replacement was made with blood and normal salt solution or dextrose in water in all cases.

RESULTS

Of the five patients in Group I there have been three deaths: The youngest patient in this group expired from cardiac failure at the age of 4½ months. Although the cause for the decompensation was recognized in this patient, his condition was too critical to permit surgical correction. Necropsy confirmed the clinical diagnosis and showed in addition a suggestive stenosis of the mitral valve. The 14-month-old patient had a technically successful end-to-end anastomosis but expired at the completion of the operation from cardiac failure thought to be due to the diminution of peripheral resistance resulting from the correction of the coarctation. It is our belief that we failed to maintain an adequate blood volume in this infant. Necropsy failed to disclose any additional cause for death. The 3-year, 2-month-old child survived the operation and was markedly improved for a month when he developed signs of cardiac failure from which he died suddenly two months after operation. Necropsy revealed evidence of acute myocardial failure, terminal bronchopneumonia, mitral stenosis and mitral valve vegetations. This valvular disease appeared to have antedated the surgery and emphasized the necessity of ruling out subacute bacterial endocarditis preoperatively. This patient had had penicillin prophylactically before surgery which might well have masked the subacute bacterial endocarditis. It is unlikely on an age basis that he had rheumatic fever. The remaining two patients in Group I are classified as having excellent results with decrease in the blood pressure in the upper extremities, palpable lower extremity pulses, decrease in heart size and achievement of normal activity.

Of the eight patients in Group II that had surgical correction of the coarctation, there has been one death. This patient (who is the only mortality in this group) probably had subacute bacterial endocarditis antedating the surgical correction of the coarctation by three months. The bacteremia was masked by the antibiotics administered for a brief period of time three months before operative correction of the coarctation was undertaken. The patient developed signs of peripheral emboli approximately one month following resection of the coarctation. Eventually an aneurysm occurred at the site of the suture line. *Streptococcus viridans* was not isolated from the blood stream until six months following the aortectomy. The patient eventually experienced severe bouts of hemoptysis and expired nine months after operation. Bacteremia was present at the time of death in spite of massive dosage of antibiotics. This patient is the only instance of an aneurysm developing at the suture line in the entire group.

Three of the patients of Group II are classified as having a good result and four as having an excellent result. In the three patients classified as having a good result, it was not possible to do an end-to-end anastomosis because of insufficient mobility to span the defect. In place of the end-to-end union, a plastic repair was done in one patient, a subclavian to aorta anastomosis, end-to-side, in the second patient, and in the third patient, the subclavian was united to the aorta, end-to-end.

These patients have had a fall in pressure in the upper extremities and a rise in pressure in the lower, but the pulse volume in the lower extremities and

the systolic blood pressure in the lower extremities are less than in the group classified as excellent. The four patients classified as having excellent results had excision of the coarctation with end-to-end anastomosis.

SELECTION OF CASES

Technically, the operation for coarctation of the aorta is feasible. The decision to operate and when surgery should be performed depend upon several factors. Evidence of cardiac decompensation caused by the inability of the heart to work against the coarctation in the absence of collateral circulation is one of the prime reasons for early surgery. Decompensation as a manifestation of coarctation should be suspected in young patients. The diagnosis could not be made in the 14-month-old child in Group I because of the generalized edema. It was following digitalization and the subesequent disappearance of the edema that the diagnosis of coarctation of the aorta could be established. Surgery in this patient was successful but the supportive therapy failed.

In patients having coarctation without cardiac failure, the factors to be considered are the hazards of subacute bacterial endocarditis, atheromatous changes in the aorta (which may preclude satisfactory union at the suture line), friability of collateral vessels which may allow spontaneous rupture, and end results of long-standing hypertension. Subacute bacterial endocarditis probably occurred twice in this group (aged 3 years, 2 months, and 14 years) and vegetations were found in two 14-year-old patients. An atheromatous plaque was found in two patients aged 10 years, 9 months, and 13 years. One patient, aged 15 years, received four units of blood because of bleeding from the friable collateral vessels at the time of operative repair of the coarctation. One of our patients had been subjected to psychiatric therapy because of behavior problems that really were caused by hypertension and claudication.

The concern that there may not be growth at the anastomotic site has caused some observers to hesitate in recommending surgery at an early age. After weighing the advantages and disadvantages, it is our practice to advise early surgery even though it may be necessary to replace the original anastomosis with a graft in later life.

Another discussed complication of the operative treatment of coarctation of the aorta is the formation of an aneurysm at the suture line. It is our opinion than an aneurysm is not likely to develop in patients repaired by end-to-end anastomosis except in the presence of subacute bacterial endocarditis.

SUMMARY

Our experience in fourteen cases of coarctation of the aorta has been presented. Twelve of these cases have had some type of surgical correction. An analysis of our material places our patients into two clinical groups. The importance of coarctation of the aorta as a cause of cardiac decompensation in children under 5 years of age is demonstrated in our Group I. Group II demonstrates the early appearance of the degenerative effects of continued hypertension.

The values of retrograde arteriography have been outlined, the methods of surgical repair reviewed, and the results detailed. Our concepts of the indications for surgical treatment of coarctation of the aorta in children are presented.

INCREASING INTERDEPENDENCE OF THE OBSTETRICIAN AND THE PEDIATRICIAN

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NOT too long ago the obstetrician and the pediatrician for any given case were usually embodied in one and the same person. Even today a considerable proportion of infants are delivered and cared for by the same physician. But the great emphasis on medical specialization of recent years has, in many areas and for many babies, totally separated the pediatric and obstetric functions required by a pregnancy. Today, it is not too unusual to find a mother and a child cared for, during and immediately after birth, by an obstetrician and a pediatrician who never even meet or speak to each other at any time during the handling of the case.

From a strictly medical point of view there is, of course, something to be said for the separate application of two different types of medical acumen to two different types of patients. Even under uncomplicated circumstances of parturition and the puerperium, both patients probably receive more expert care than they could hope for from the services of one physician in whom pediatric and obstetric knowledge are combined. The very size of the body of knowledge in each field makes it difficult, if not impossible, for a single physician to assimilate and use it as satisfactorily as can separate specialists.

It is equally obvious, however, that this separation of the specialties raises definite problems in the over-all management of the childbearing woman. For a time, in the early days of specialization, such problems were not of great enough moment to give serious concern; the overlapping of the pediatric and obstetric fields was not extensive enough to demand special attention. In recent years, however, newer knowledge of the reciprocal relationship between maternal and fetal status has tended to increase the extent of the whole problem. This is especially evident in the realm of psychologic and psychosomatic aspects, to which so much of our attention has been turned in the past decade. So many obstetricians and pediatricians today increasingly encounter troubles arising out of this incoordination of their care that it is not inappropriate to examine the matter specifically with a view to improving the whole medical and psychological status of both the mother and her newborn child.

THE OBSTETRICIAN'S RESPONSIBILITIES TO THE PEDIATRICIAN

So far as strict physiology and pathology are concerned, the well-informed obstetrician today recognizes an increasing pediatric responsibility in terms of the quality of the infant he delivers. Not too long ago we tended to regard the fetus as a relatively passive package, not greatly affected by the conduct

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of routine prenatal care. Obstetrical problems, especially in the fields of infection, hemorrhage, and toxemia, were so tremendous that the prime concern was for the mother's life and health, and where conflicts between these and the interests of the fetus arose, scant consideration could be given to the baby. The problem of infection has very largely yielded to refined obstetric techniques and the antibiotics; the problem of hemorrhage has been minimized by the increasing availability of blood; and the control of toxemia has improved with more general prenatal care and our slowly increasing understanding of the disease itself.

We find ourselves, then, as obstetricians, thinking more and more of obstetric management in terms of effect on the fetus. This is exemplified, in early pregnancy, by such complications as rubella, and hemorrhagic disease of the newborn. The whole question of maternal nutrition during pregnancy begins to take on new aspects in the light of recent knowledge regarding its effect on the child, the "pediatric status" of the newborn infant. In late pregnancy the obstetric approach to such complications as placenta previa, abruptio placentae, and toxemia has been materially altered by fetal considerations. When we come to an examination of methods of delivery, it is obvious that our thought is influenced to a much greater extent than ever before by our increasing knowledge of the effect of various delivery procedures on the fetus, rather than by concern about their effect on the mother. The continuing active study of various types of pain relief during labor and delivery is very largely a reflection of obstetric concern for the fetus, now that the risk to the mother has become so small in modern hands. The increasing safety, for the mother, of cesarean section has led to a general re-examination of the indications therefor, a re-examination which increasingly takes into account the interests of the baby.

While it is clear that the obstetrician must of necessity think increasingly in pediatric terms, he has perhaps been somewhat slow to pass on his information to his pediatric colleague *during the course of pregnancy.* In all probability this is not a very important omission where strictly medical problems are concerned—so long as the pediatrician is well informed of what to expect at the time he takes over the care of the child after delivery. It is conceivable, however, that much might be gained if the obstetrician were to transmit significant findings affecting the possible fetal outcome to the prospective pediatrician as they made their appearance. This is more particularly true in the psychologic and psychosomatic realm. Yet today it is generally customary for the patient to delay selection of her pediatrician until after parturition is complete.

THE PEDIATRICIAN'S RESPONSIBILITY TO THE OBSTETRICIAN

Again, so far as strict physiology and pathology are concerned, there is very little that the pediatrician can offer during the course of pregnancy or delivery—except insofar as his research studies of newborn infants may make certain prenatal and delivery procedures seem desirable or inadvisable.

Immediately after delivery, however, the problem of proper resuscitative procedures arises—initial care of the infant as it establishes extrauterine exist-

ence. Traditionally this task has fallen to the obstetrician since he is, so to speak, closest to the scene of action. This custom has its drawbacks, however, and very little in the way of advantages. During the third stage of labor, when the mother requires the obstetrician's most skillful services, his attention is often diverted to coaxing an initially wobbly baby into vigorous function. Moreover, his efforts frequently go unthanked, for the pediatrician who later takes over may often be heard to grumble about the trauma to which his new patient was subjected during resuscitation.

Indeed, the question of just when pediatric care should begin is still an open one. A few pediatricians have taken it upon themselves to be present at the delivery of their patients. Sticking to this arduous resolve (though pediatricians, after all, are as accustomed to night work as are obstetricians) they become very skillful at resuscitative techniques, and those of us obstetricians who have encountered this blessed breed of pediatrician have been most grateful to them for taking over a sometimes worrisome responsibility at a time when our hands are full.

Later on the problem of breast feeding is one which very definitely impinges on the purviews of both the obstetrician and the pediatrician. Yet it is astounding how many pediatricians and how many obstetricians, both caring, so to speak, for the same patient-pair, never make any attempt to exchange their respective thoughts or to compromise their differing attitudes on this question. The obstetrician may have spent several months gradually bringing his patient to an acceptance of a trial of nursing only to be stymied by a pediatrician who attaches little importance to it one way or another. Or, the obstetrician may have accepted, without further ado, his patient's initial refusal to consider breast feeding, only to find that the pediatrician, called in after delivery, is horrified at what he feels to have been inadequate attention given to the matter. The very nature of the nursing process, and its implications for the maternal reproductive tract and mammary system as well as for the infant, is one which demands that the obstetrician and the pediatrician present to the patient consistent attitudes regarding it. It is difficult to see how such consistency can be satisfactorily reached in a hit-or-miss fashion at the last minute. And when inconsistency is manifest, as it so often is, the effect on the mother, both psychologic and, as it were, lactational, can scarcely be a beneficial one.

PSYCHOLOGIC AND PSYCHOSOMATIC ASPECTS

While the increasing overlap of pediatric and obstetric functions is apparent to some degree in the physiologic realm, its effect is undoubtedly felt most acutely in the psychologic and psychosomatic aspects of pregnancy, parturition, and neonatal care. Intuitive obstetricians have long recognized that during pregnancy, both literally and figuratively, the mother does not live by bread alone. In recent years more specific studies of the psychologic aspects of childbearing have found their way into print with increasing frequency. Obstetricians familiar with this type of inquiry find continual affirmation of two basic principles: (1) that physiologic care of the pregnant

woman is not enough; her psychologic problems must also be met; (2) that psychologic disturbances (today, almost universal in their occurrence) very frequently exert a significant effect on the actual physiology of pregnancy and parturition.

It is the increasing insistance favoring these two principles which has led to the steadily growing emphasis on varoius types of pre-pregnancy and prenatal psychologic management of prospective parents. At one extreme we have the Grantley Dick Read approach, highly individualized, time consuming, and expensive, but with meticulous attention to individual psychologic problems. At the other extreme we find the routine type of "mothers' class" which attempts primarily to correct the mother's factual ignorance, but which also, in the process, accomplishes a not inconsiderable psychologic function. (Actually, at the other extreme we have the medieval obstetrician who cares not a whit how his patient reacts emotionally to, and during, pregnancy but is interested only in what she eats, how she sleeps, and so on.) Somewhere in between we find the private obstetrician, struggling, in the limited time at his disposal, not only to keep a careful eye on his patient's blood pressure, urinalysis, and the like, but also to give some attention to the fears, conflicts, resentments, and other psychologic disturbances which beset her. On his failure or success in the latter endeavor may depend to a considerable degree the amount of the patient's somatic symptomatology, the progress and nature of her pregnancy and delivery.

In the course of this psychologic management two things very soon become apparent: (1) much of the patient's psychologic disturbance during pregnancy, labor, and delivery may be directly concerned with her attitude toward her baby and her thoughts about its care and nurture after its arrival; (2) a better opportunity for specific psychologic preparation of a mother (indeed, of a "pregnant couple") for well-adjusted, beneficial child rearing presents itself during pregnancy than after the baby has arrived. (Actually, of course, preparation for child rearing starts in the infancy of the mother and father, but often the first opportunity for a knowledgeable influence on this preparation is given to the obstetrician during a first pregnancy.) It is in this latter sense that the term "prenatal pediatrics" is most applicable. In connection with the first statement we might coin the term "pediatric obstetrics," indicating that preparing a mother well, both informationally and psychologically, to undertake the care of her expected child may be tremendously beneficial to the actual course of pregnancy and parturition.

It is obvious that both of the foregoing statments define problems of a psychologic, psychosomatic nature which devolve at present upon the obstetrician, but which are very largely pediatric in nature. The question then arises as to how much of a part in their solution the pediatrician should play *during the course of pregnancy*. The very term "prenatal pediatrics" suggests that he should have a considerable role; and the term "pediatric obstetrics" suggests that his efforts during pregnancy may be of immense aid to the obstetrician.

It is our contention that pediatricians in general have not gone nearly far enough in taking on this new task. Psychologically-orientated pediatricians who are interested in child behavior have drummed at us the fact that infant, and later, behavior problems stem from the parents, not from the child. Yet for the most part they have waited until the newborn child is dropped into their laps before making any efforts to treat the problem-parents. On the other hand, obstetricians, always loath to have others trespass on their domain, have made little effort to call in the pediatrician during pregnancy for the current and future benefit of the parents and child. It would seem that in this sense a golden opportunity for making a closer approach to "normal" obstetrics and "normal" pediatrics is still going begging.

Where the private, individual practitioner of obstetrics and of pediatrics is concerned, it would seem evident that an early selection of the pediatrician by the patient and the obstetrician is highly desirable. And this selection should fall upon a pediatrician who is willing to see the prospective mother of his later patient *early in pregnancy*. Moreover, it is assumed that he and the obstetrician will be eager to discuss between themselves the psychologic and physiologic problems which may thus be solved not only during the course of pregnancy, but also for the future.

POSSIBLE METHODS

The foregoing statement is easy to make. Its actual application, however, involves so many practical problems that they seem almost insurmountable. The practicing obstetrician and pediatrician today find their time so fully occupied—with more demands upon it always waiting in the offing to pounce upon them—that a proposal such as the one suggested above can scarcely be taken seriously by them. Yet the need is obvious. What possible solutions are there?

The group practice of medicine offers one feasible means of accomplishing our aim. We realize that group practice is anathema to many quarters at the present time and that a mention of it may occasion lifted eyebrows. Nevertheless, it would be ostrichlike not to admit that there is a good deal of group practice of one sort or another extant in this country at the present time. It would be equally short-sighted not to examine this form of medical practice in terms of what special benefits it *can* offer, in spite of whatever drawbacks it is said to possess.

Such examination shows that the very physical set-up of a group practice makes a good effort at prenatal psychologic management possible for both the obstetrician and the pediatrician. Throughout their working hours they are in such close proximity that not only are both of their services available to patients all of the time, but they also have easy opportunity to confer between themselves about the psychologic problems of their patients.

This is scarcely the ideal solution, however. For even under the circumstances of group practice the carrying out of a program of psychologic management will place a tremendously increased demand upon the time of both the obstetrician and the pediatrician, especially the latter. This increased

demand must, of course, be reflected in increased cost to the patient in the long run, and costs are bad enough as they stand at present.

We must turn, it would seem, to some sort of program which makes use of *groups of patients.* We return again to the old idea of "mothers' classes." But in returning to it let us not go back to an old routine which loses sight of the type of thing we really want to accomplish with and for our modern child-bearing families. The earlier mothers' classes contended themselves with instructing women in the simple practicalities of prenatal care. They inculcated a skeleton amount of purely mechanical pediatric information. They ignored husbands entirely as though fathers had no stake whatever in the future of their offspring. They were generally conducted, not by physicians, but by ancillary personnel who were scarcely inspiring, carried little authority, and were not well enough equipped to cope with the vital area of psychologic counselling.

Fortunately, the more modern attempts to carry out prenatal education for groups of patients have been more promising. They take the form of "parents' classes," or better yet "parents' conferences," the latter title carrying the implication of active parent participation. They make fuller use of our much more extensive knowledge of teaching techniques—visual aids, demonstrations, practice sessions, participation programs, and the like. To be sure, they depart to a considerable degree from our cherished principle of individualization of patients. But in another field, psychiatry, physicians have already begun to discover that individualization of patients solves problems only up to a certain point; beyond that there simply are not enough psychiatrists to go around. So in the purest field of psychologic management of all, we already begin to see mass counselling techniques being tried out here and there. The problem in the obstetric-pediatric field is exactly similar.

At the University of California Hospital we have had a brief two years of experience with a modernized program of parents' conferences (for both clinic and private patients). The organization of it is still, of course, in a rudimentary stage. But we have placed special emphasis on an attempt at group psychologic counselling and on the participation in the program of pediatricians. While we are hardly in a position to make a solid evaluation of the benefits of our program, tentative analysis seems to suggest its definite value, at least from an obstetric point of view.[1] Evaluation of its pediatric benefit will assuredly be a complex and long-term study. Moreover, a considerable expansion of the pediatric portion of our program appears to be indicated in the light of our developing experience. We must confess, indeed, that in our own program the golden opportunity for prenatal pediatrics is still going begging to some degree. Hence, perhaps, our continual reiteration of the importance of seizing it.

One may well ask, however, what all this has to do with the individual practitioner of obstetrics and pediatrics. Our answer would be that it is perfectly feasible, in a given locality, for private practitioners to group together for the purpose of organizing prenatal parent education for all of their patients, the instruction to be carried out *en masse* in large classes. While this

may seem doubtful at first glance, we already know of three such experiments which seem to be working satisfactorily. The physician-participants soon discovered that their fears regarding the "losing" of patients to one another proved to be groundless.

We come, in the end, to the fact that if obstetricians and pediatricians are truly and deeply interested in the best preparation of couples for parenthood, both physiologically and psychologically, then methods will be found for accomplishing it which are economical, practical, timesaving, and effective. At the present time prenatal parent education for large groups of patients seems to offer the greatest promise. It will call for the best thought and the most cooperative efforts of obstetricians and pediatricians.

SUMMARY

The present directions taken by the specialties of obstetrics and pediatrics seem to indicate a progressively increased overlapping of the fields, especially where psychologic and psychosomatic aspects are concerned. It behooves obstetricians and pediatricians to give more thought to the development of planned, cooperative programs, starting early in pregnancy, designed to give the most expert attention to these areas of mutual responsibility. It seems certain that such programs will benefit not only the mother during childbearing but also her newborn infant.

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FURTHER OBSERVATIONS ON THE ANTEPARTUM PREDICTION OF HEMOLYTIC DISEASE OF THE NEWBORN

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DURING the last several years, there has been an increasing tendency to disregard laboratory findings in making predictions as to the fetal outcome in women who are sensitized to the Rh factor. Some authors maintain that the only significant fact is the history of sensitization, either by transfusion of Rh-positive blood or by the birth of a child afflicted with hemolytic disease. It is perfectly true that such a history is of considerable import, but it may be difficult to obtain in some instances, and is obviously missing in those women who give no history of transfusion and who, for the first time, give birth to infants afflicted with hemolytic disease. On the other hand, sensitization to the Rh factor in any pregnancy is almost always reflected by the laboratory findings, and prior sensitization is quite invariably indicated by the presence of Rh antibodies early in the course of gestation.

There are other reasons for an attitude of distrust about the prognostic significance of antepartum blood tests. So long as the antibodies exist to any significant degree, there is only a moderate relationship between the actual quantity present and the fetal outcome. A rapid fall or rise in the titer during the last month is not necessarily of significance. Furthermore, when a husband is heterozygous, there is no laboratory method at present which will inform us in advance whether a woman, previously sensitized, is carrying an Rh-negative or an Rh-positive baby.

On the other hand, when several observations are taken into consideration simultaneously, the laboratory findings become of considerable prognostic significance and are of greater value than the history alone. It has been pointed out by Lucia and Hunt[1] that 4.3 per cent of an unselected sample of Rh-negative women bear infants suffering from hemolytic disease, but that 45.4 per cent of those showing any evidence of sensitization before delivery produced babies afflicted with the disease. These facts alone make it imperative that we examine the blood of the obstetrical patient before delivery, for the absence of antibodies insures the absence of hemolytic disease (except in those very rare instances due to factors other than Rh), while the mere presence of antibodies means that we may expect difficulties in half the patients.

There is much more, however, that we may learn from such tests. It was pointed out by Page, Hunt, and Lucia[2] that the length of time the antibodies existed before birth was of prognostic importance, and that the critical period of time was about ten weeks. This has been confirmed by Murray and Taylor[3] who found that in twenty-two cases where antibodies existed in the first half

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of pregnancy, all babies were affected and only five survived; whereas in eleven cases in which antibodies were not present at sixteen weeks but appeared after the thirtieth week, all babies survived.

Sacks, Kuhns, and Jahn,[4] on the other hand, concluded from their data that the degree of sensitization was more important than the duration. Primrose, van Dorsser, and Philpott[5] believed that both the degree and the duration of sensitization may be plotted graphically in such a manner as to make reasonably accurate predictions. Potter,[6] in her very complete book on the Rh factor, does not discuss the question of antenatal prognosis.

In a recent study, Lucia and Hunt[7] point out that there are at least five observations which should be taken into consideration. They are, in the order of importance, as follows:

1. Definitely higher amounts of maternal Rh antibodies when tested in albumin solution than in saline. (This confirms the observations of Weiner[8] and of Diamond and Denton[9] regarding the serious significance of "blocking" antibodies.)

2. An appreciable amount of antibodies (3+ or over) in the maternal serum during the last month before delivery.

3. The appearance of the antibodies more than ten weeks before delivery.

4. The presence of antibodies on every successive testing after their first appearance.

5. The presence of ABO compatibility between mother and baby. (A detailed analysis of this observation is presented in a separate report.[10])

In order to assess the importance of these five laboratory observations, we have selected sixty-two women on which all of these data are available, excluding only those patients who demonstrated small amounts (i.e., a "trace" or 1+) of antibodies inconsistently during pregnancy. We have found that inconsistent traces of antibodies may be ignored so far as the fetal outcome is concerned. The presence or absence of hemolytic disease, in relation to each of these five factors, is summarized in Table I. Of the thirty-four normal infants, ten proved to be Rh-negative children born of mothers previously sensitized, and these are listed separately in order to show that we cannot make this prediction before birth.

TABLE I. THE NUMBER OF BABIES WITH OR WITHOUT HEMOLYTIC DISEASE OF THE NEWBORN (H.D.N.) WHO WERE POSITIVE FOR EACH OF FIVE ANTENATAL MATERNAL FACTORS

CONDITION OF CHILD	NO.	RH ANTIBODY HIGHER IN ALBUMIN	ANTIBODY TITER 3+ OR OVER	ANTIBODY DURATION OVER 10 WEEKS	CONSISTENTLY PRESENT	MOTHER AND BABY ABO COMPATIBLE
Afflicted with H.D.N.	28	27	28	27	28	28
Not afflicted with H.D.N.						
Rh positive	24	6	14	17	18	20
Rh negative	10	6	9	10	10	7

The recapitulation in Table II presents the salient features which we wish to stress in this analysis. Of the twenty-eight infants suffering from hemolytic disease, only two mothers failed to show all five factors prior to delivery. In one of the instances, the "saline agglutinins" appeared to equal the quantity in albumin diluent (presumably indicating an absence of blocking antibodies), and in the other case, antibodies were detected less than ten weeks before delivery.

TABLE II. THE NUMBER OF BABIES WITH OR WITHOUT HEMOLYTIC DISEASE OF THE NEWBORN (H.D.N.) WHO LACKED A GIVEN NUMBER OF THE FIVE ANTENATAL MATERNAL FACTORS

CONDITION OF CHILD	NO.	THE NUMBER OF FACTORS LACKING (I.E., "NEGATIVE")				
		NONE LACKING	ONE LACKING	TWO	THREE	FOUR
Afflicted with H.D.N.	28	26	2	0	0	0
Not afflicted with H.D.N.						
Rh positive	24	2	5	11	6	0
Rh negative	10	4	5	0	1	0

Of the thirty-four women who bore healthy babies, only six showed all five factors. Four of these are readily explained by the fact that the infants were Rh negative, while in the remaining two cases, no explanation is available. It is possible, of course, that these two babies were of different genotypes than the blood which had produced prior sensitization.

Suppose now that one is dealing with a woman near term and has performed the necessary laboratory tests to give information regarding the five factors mentioned. If all factors are "positive," and the husband is known to be homozygous for the Rh factor, the odds are fourteen to one (93 per cent in this series) that the baby will be afflicted with hemolytic disease. Should the husband be heterozygous, the odds are only nine to eleven, for half of the babies will escape the disease through their failure to inherit the Rh factor, and one out of ten may escape by virtue of some genotypic difference or possibly for some reason as yet obscure.

If one factor is "negative," this series would suggest that only one in thirty babies will be affected, and if two factors are missing, it is almost certain that the baby will be healthy.

It is not only for the purpose of being prepared for the birth of a child with hemolytic disease that such predictions are important. This, to be sure, is sufficient reason, for Allen, Diamond, and Watrous[11] have shown that an exchange transfusion using blood from a female donor (possibly from those Rh-negative women who have borne Rh-positive babies without being sensitized) offers an excellent prognosis for the infant even when the disease is severe. Predictions are also important for the evaluation of any type of antenatal therapy which may be used experimentally. Many procedures have been suggested for the prevention of hemolytic disease, such as the injection of a "hapten" made from Rh-positive cells as proposed by Carter,[12] the use of a "competing antigen,"[13] the use of methionine,[14] or even the administration of one tablet of anhydrohydroxyprogesterone daily with some vitamin K.[15]

Unless the incidence of the disease can be significantly reduced in babies born of those mothers who show *all* the laboratory findings which characteristically precede the birth of children with hemolytic disease, such treatments must remain open to serious question.

While the laboratory findings, together with the history of sensitization whe.. available, give us important clues as to the presence or absence of hemolytic disease in babies yet to be born, they are less reliable indicators of the severity of the disease. To be sure, a greater amount of blocking antibody existing for several months is a grave omen, but we have been pleasantly surprised on occasions to find that the babies are not as seriously damaged as we anticipated. Whether this was due in some cases to the induction of labor three or four weeks before term is problematical, but we feel that this is still an open question and one which deserves further investigation. Murray and Taylor[3] believe that elective induction of labor several weeks before term has been of value, while both Potter and Diamond have expressed a disapproval of this practice. The question of the survival and good health of the babies is dependent not only upon the severity of the illness, but the form of therapy administered after birth. The fact that therapy is rapidly improving should not make us overlook the possibility of trying to reduce the seriousness of the disease by shortening the time of exposure to the antibodies, or by some form of antenatal treatment of the mother. The problem may only be resolved when carefully controlled series of sufficient size are available in which only one variable (such as induction or noninduction) represents the difference. From the obstetrical viewpoint, it does appear that if induction should be selected as a method of treatment, cesarean section is of no advantage in the multiparous woman. In fact, Wiener and Wexler's data[16] show a much higher fetal mortality in the erythroblastic babies delivered by cesarean section. They appear to favor the induction of labor before term.

SUMMARY

The routine testing for Rh sensitization, throughout every Rh-incompatible pregnancy, is of definite value in the antenatal prediction of hemolytic disease of the newborn. This is especially true when five factors are taken into consideration: (1) the presence of "blocking" antibodies, (2) a significant quantity of antibodies, (3) their existence for more than ten weeks before delivery, (4) their presence on every successive test, and (5) the presence of ABO compatibility between mother and baby. When all five factors were "positive," only two out of twenty-eight Rh-positive babies escaped hemolytic disease. If but one factor was "negative," twenty-eight out of thirty babies escaped the disease, and if two factors were missing, all babies were healthy.

Such predictions have been of value in planning neonatal therapy, and should be of great assistance in evaluating the effects of early induction of labor or the benefits resulting from any type of antenatal therapy.

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INFECTIOUS MONONUCLEOSIS OF THE CENTRAL NERVOUS SYSTEM WITH BILATERAL PAPILLEDEMA

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IN 1941 a case of infectious mononucleosis with meningitis[1] was reported from our service. A review of the literature at that time revealed relatively few cases with central nervous system involvement in the form of spinal fluid pleocytosis, encephalitis, or paralysis. Ten cases were cited. In the article were described two cases which did not fully conform to infectious mononucleosis and which in view of later elucidation probably were infectious lymphocytosis with meningitis; this view has been expressed by numerous authors discussing infectious lymphocytosis in recent years.

Reports of cases of infectious mononucleosis complicated by central nervous system disease have continued to appear. These have varied in degree and in type of involvement. There have been several additional cases of serous meningitis.[2-5] Other cases have shown primarily encephalitis or encephalomyelitis.[6-17, 22]

In a few instances there has been a striking albuminocytological disassociation in the spinal fluid. Two of these had neuromotor and sensory changes characteristic of the Guillain-Barré syndrome.[11, 17] Even isolated muscle weakness thought to be due to central nervous system involvement has been reported.[18, 19] Three deaths attributable to diaphragmatic and intercostal paralysis have been recorded.[11, 22]

One patient with encephalomyelitis had considerable residual muscle weakness, sensory changes, and signs of cerebellar damage many months after apparent recovery from the acute process.[8]

In many of the protocols there is no reference to examination of the retina. Presumably in many of these such examination revealed no abnormality and was omitted from the report. In several instances ophthalmoscopic examination is recorded as normal or as showing slight hyperemia of the retina. In 1947, however, Ashworth and Motto[20] reported infectious mononucleosis in a 19-year-old soldier who had 3+ diopter papilledema, noting that this was the first case recorded without accompanying meningitis or encephalitis. The patient's optic complaints were pain on downward and lateral movement of the eyeballs, symptoms present in the patient reported in the present paper. In Gesell's[4] report of three cases of infectious mononucleosis with serous meningitis he describes optic neuritis in one. It is also interesting that Clemens,[21] in 1907, reporting on an epidemic of "glandular fever," lists seven cases with hyperemia of the discs and/or optic neuritis. The epidemic that Clemens describes, in view of what is now known about infectious mononucleosis, cannot be accepted

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as necessarily due to the same etiological agent. Even the report of blood studies is meager, consisting of a single statement that most of the blood counts revealed a leucocytosis.

The following case report describes a patient with severe encephalomyelitis with bilateral papilledema complicating infectious mononucleosis.

CASE REPORT

R. G., a 21-year-old white male patient, entered the Children's Hospital on July 10, 1949, with a tentative diagnosis of poliomyelitis. Two days prior to admission he had fever, sore throat, and headache. On the morning of entry he developed a stiff neck and inability to stand and walk.

He had always been well except for moderately severe giant hives experienced in childhood after receiving tetanus antitoxin and occasional episodes of hay fever.

His family history was negative.

Physical examination on entry revealed a well-formed, robust young man who was seriously ill with fever of 38.8° C., membranous tonsillitis, and neck and back stiffness. There was marked generalized weakness of both lower extremities. The right knee and ankle jerks were present but were very sluggish. The fundi were normal. The spleen was not palpable.

Laboratory Examination.—Entry laboratory studies revealed: red blood cells 5.8 million; hemoglobin 16.8 Gm.; white blood cells 17,600 of which 40 per cent were polymorphonuclears; of these 22 per cent were nonfilamented, and 18 per cent filamented; 56 per cent were lymphocytes; 2 per cent were monocytes; 2 per cent were unclassified, but were not characteristic of infectious mononucleosis.

The urine was negative except for a trace of albumin with from 2 to 3 red blood cells and an occasional white blood cell per high power field.

The sedimentation rate was 8 mm. per hour (Wintrobe, corrected). The Kahn test was negative. The Kolmer gave a 2-plus reaction in the first two dilutions. The control was negative. Throat culture revealed alpha hemolytic streptococci and rare pneumococci. No Klebs-Loeffler organisms appeared. The tuberculin test, using old tuberculin, strength of 1:10,000, was negative.

The cerebrospinal fluid was clear and had normal dynamics. There were 233 white blood cells, of which 30 per cent were polymorphonuclears and 70 per cent were mononuclear cells. The cerebrospinal fluid protein was 100 mg. per cent, and the sugar 68.5 mg. per cent. Smear and culture of the fluid were negative.

The patient was given 300 c.c. of irradiated plasma on each of the first two hospital days and Crysticillin 300,000 units daily for the throat infection.

He continued to have a fever ranging between 38.0° C. and 40.0° C. until the eleventh day of his illness, after which he was completely afebrile.

He developed urinary retention by the night of entry and was unable to void spontaneously until the ninth day of the disease.

During the first three days the neck and back stiffness increased and the weakness in the legs became more pronounced. On the fourth hospital day, the sixth day of his illness, the white tonsillar exudate was found to have increased in amount in spite of intramuscular penicillin. The spleen had become palpable. The white count was 14,800 with 56.5 per cent lymphocytes, some of which were highly suggestive in appearance of infectious mononucleosis. Heterophile antibody titer was found to be strongly positive in a dilution of 1:1,280 and slightly positive in a dilution of 1:3,200.

The patient was given 5.0 c.c. of immune globulin on the fifth day and this dose was repeated on the next day.

For the next four days there was rapid clearing of the tonsillar exudate and a considerable return of muscle power in the lower extremities. A complete blood count on the tenth day of the illness revealed a further increase in lymphocytes up to 65 per cent, many of which had typical infectious mononucleosis morphology.

On the eleventh day definite saddle hypoesthesia was found, but the rest of the sensory examination was negative. From the onset of his disease, the patient had visual difficulties characterized by impairment in reading and in recognizing people at a distance. He complained of double vision on at least one occasion. Eye pain on lateral and downward gaze was marked around the tenth day. On the thirteenth day of his disease the patient had on careful examination of the visual fields some restriction of the right nasal field. Ophthalmoscopic examination by Drs. S. Malin and J. Bramham of the resident staff revealed definite papilledema of both discs.

Muscle power in the lower extremities completely returned between the thirteenth and the sixteenth day accompanied by the occurrence of hyperactive deep tendon reflexes, bilateral ankle clonus, and positive Babinski's reflexes. The blood pressure was moderately elevated, 140/90-110. The nonprotein nitrogen was within normal limits (26.2 mg. per cent). The cephalin cholesterol flocculation was 4 plus.

On the eighteenth day Dr. C. Allen Dickey, consulting ophthalmologist, described the presence of bilateral papilledema of 2-plus diopters as well as some extravasation of blood around the inferior nasal artery of the right fundus. The maculae appeared normal. No other retinopathy was noted.

On the nineteenth day, the heterophile agglutination was positive in a dilution of 1:320 and slightly positive at 1:1,280. The Kahn and Kolmer tests in all dilutions were negative. Repeat lumbar puncture revealed clear fluid with normal dynamics. The cell count was 10, all mononuclears. The protein was 59.3 mg. per cent. The spinal fluid Kolmer was negative and the Lange 2,2,2,2,2,1,1,1,1,1.

Serologic studies done by Dr. W. McD. Hammon at the Hooper Foundation, University of California, revealed negative complement fixation tests for Western and St. Louis encephalitis, and for Newcastle disease virus. Complement fixation test for mumps virus was positive (titer 1-16) with no later rise in titer, indicating previous contact with mumps virus. Neutralization test was negative for viruses of Western equine and St. Louis encephalitis.

From the eighteenth to the twenty-eighth day of his illness, the day of discharge, muscle power continued to improve, although the deep tendon reflexes remained hyperactive and the Babinski's positive. The papilledema decreased slightly. Sensory perception was improving in the saddle area. The spleen remained palpable about three fingerbreadths below the left costal margin. On the day of his dismissal the patient was subjectively well and ambulatory.

When examined approximately a month after discharge, the patient was without symptoms. The spleen was not palpable, the deep tendon reflexes were normal, and no clonus was obtained. Dr. Dickey reported: "Examination showed his uncorrected visual acuity to be R-20/20, L-20/20; muscle balance for distance and near vision was normal; extraocular movements: normal; convergence: normal. Central field examination was normal and there was no evidence of enlargement of the blind spot. Fundus examination disclosed that there was still a slight blurring of the superior margins of both discs. There was one minute hemorrhage remaining above the right disc. Apparently this boy has almost completely recovered from his papilledema and there is no further evidence of ocular pathology."

DISCUSSION

This case is arresting not only because of the many and marked associated neurological findings but also because of the presence of frank papilledema. The sparsity of evidence of increased intracranial pressure sufficient to produce the nerve head changes described in this and other cases, leads to the assumption that the papilledema represents a primary optic neuritis. Fortunately the reports to date indicate that recovery tends to be relatively prompt and complete.

It is obviously important that the eye grounds of patients with infectious mononucleosis, with or without central nervous system involvement, be examined repeatedly through the course of the illness in order to clarify further this manifestation of the disease.

Papilledema complicating infectious mononucleosis adds further weight to the growing impression that this disease, once passed off jocularly as the "medical student's disease" and respected mostly for its nuisance value, is in fact a protean illness of no mean magnitude. Because it is occurring more frequently than previously suspected, affects a greater age range than was once apparent, and produces alarming central nervous system disturbance in an acute and passing form, possibly in a permanently damaging way, it is a disease that must be studied further energetically as to etiology, prevention, and treatment.

The use of both plasma and immune globulin in this case seemed justified in light of the known severity and bad outcome in some cases of infectious mononucleosis of the central nervous system and the lack of any other effective therapy. It is impossible to evaluate any effect from such therapy since a weak or doubtfully potent agent is employed in a disease of unpredictable course.

SUMMARY

The literature pertaining to central nervous system complications in infectious mononucleosis is briefly reviewed.

Serous meningitis occurs moderately frequently and will be manifested by nuchal rigidity, headache, and pleocytosis of the spinal fluid, which symptoms and signs may occur as an isolated finding or in varying combinations.

Cases of encephalitis and encephalomyelitis due to infectious mononucleosis in which there is nervous tissue damage with or without associated meningeal disease are not uncommon.

Papilledema, probably primary optic neuritis, complicating infectious mononucleosis with or without serous meningitis or encephalomyelitis has been described.

A detailed report is given of a case of infectious mononucleosis complicated by serous meningitis, encephalomyelitis, and papilledema.

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VOLUNTARY IMITATIVE CONVULSIVE ATTACKS OBSERVED IN A CONVULSIVE CLINIC

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INVESTIGATORS of the convulsive state in infants and children are aware of the emotional components that influence the course and therapeutic results of treatment. In their observations, Jensen,[1] Bradley,[2] and Kanner[3] have discussed the necessity of dealing with maladjustment and emotional components in an endeavor to obtain optimum therapeutic results. In a convulsive clinic, limited to the treatment of convulsions in infants and children, one realizes that not only the patient enters into the investigation but also the family unit. Awareness of the parents' reactions to the complaint factor is as important as many of the diagnostic procedures utilized in the work-up of a case of convulsive state.

During the past ten years one thousand cases of convulsive state have been referred to the convulsive clinic within the Division of Pediatrics. All of these cases have come under my observation and study. The two cases reported here are rather unique in my experience. In both cases the patients demonstrated that they could voluntarily imitate convulsive attacks which appeared real to both parents and physician.

CASE REPORTS

CASE 1.—E. W., a 6-year-old white female, was referred to the Pediatric Out Patient Department by her private physician, with the complaint of petit mal attacks. At the time, she was experiencing fifteen attacks daily. The type of spell described was a typical petit mal seizure. Her physical, including neurological, examination was essentially normal, with the exception of a typical petit mal attack which could be precipitated by hyperventilation. The electroencephalogram corroborated the diagnosis of petit mal seizures. A psychometric examination, using the Stanford-Binet Form L, revealed an I.Q. of 96. During the test procedure the psychologist observed two typical petit mal seizures. The patient was placed on various anticonvulsive drug and dietary regimens, as well as experimental dyes, without too much success. Her attacks decreased to eight to ten daily for a time and suddenly increased, according to her mother, to thirty to fifty daily. At this time, she was referred to the Convulsive Clinic.

The patient's mother, during the first interview, indicated marked concern regarding her daughter's attacks, especially fear of mental dullness and other stigmata of epilepsy. Subsequent interviews revealed a marked overprotectiveness on her part, as well as an intense guilt feeling. Her guilt revolved around her leaving the patient with her sister for a period of three years while she and her husband participated in war work. When the parents established a home with their child, the patient's "trancelike spells" increased in number. She protested against leaving her aunt and going to live with her parents. Needless to say, this protest caused a marked emotional response from Mrs. W., and under-

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mined her feeling of certainty in dealing with her daughter. Mrs. W. described herself as being a "Calamity Jane" and other aspects of child care added to her anxiety; namely, elimination and eating. Every time she attempted to limit or help her daughter in their living relationship, she was stopped by the increase in the number of attacks. At times Mrs. W. displayed irritation and anger with the physician's inability to control her daughter's attacks with medication. She often needed support and reassurance in her role as mother. Mrs. W.'s guilt would become intensified when her daughter would ask for assurance that she would not be separated from her, and she would become quite depressed and say: "I did leave her once." Interviews with mother and child extended over a period of one year, during which time the patient's mother became more accepting of her daughter's feeling and of her own feelings regarding her daughter's complaint.

Interviews with E.W. in a play therapy setting progressed rather slowly at first, as she allowed only a little of her own feeling to enter into the play hours. She was extremely aggressive and questioned every limitation imposed —such as rules of conduct and use of materials. During this period, a number of typical petit mal seizures were witnessed, which were accompanied by circumoral cyanosis and some disorientation in the postconvulsive phase which lasted one to two seconds.

During our sixth interview she was playing with a ball when she stated: "I can roll my eyes and shake my head any time I want to. I don't have to if I don't want to." She then demonstrated her ability to imitate an attack, which was most realistic—sans cyanosis and disorientation. Later during the hour she experienced a typical petit mal seizure with the described cyanosis and disorientation. In subsequent interviews she brought out her feelings about being ill and how much she disliked it. After the patient's demonstration of a voluntary attack, her attack rate dropped in number from thirty daily to three or four attacks daily. On questioning as to how she learned to roll her eyes and shake her head, she confided that she had watched her mother show doctors the "head shaking spells" and also ladies "who are friends of mother's," and added: "mother doesn't like to see them." When asked what the mother did when she saw them, she laughed and replied: "She gets me to lie down and waits on me." After this, the patient made no further referral to her voluntary attacks, yet she did experience several petit mal seizures in subsequent interviews.

CASE 2.—K. T., a six-year-old white female, was referred to the Pediatric Out Patient Department with the complaint of petit mal seizures. She had experienced these attacks since the age of 4 years, but recently they had increased in number from twenty to forty attacks daily. The mother's history revealed hemorrhage due to partial placenta previa in the seventh month of her pregnancy. In order to reach term successfully, she was confined to bed rest for the last two months of her pregnancy.

The patient's physical examination was essentially normal, with the exception of precipitation of a typical petit mal seizure with hyperventilation. The electroencephalogram corroborated the diagnosis of petit mal attacks. A psychometric examination, using a Stanford-Binet Form L test, revealed an I.Q. of 111. During her psychometric test, she experienced five typical petit mal seizures. She was placed on Tridione 0.3 Gm. three times a day, without change in frequency of her seizures. At this time, she was referred to our clinic.

In the interview, Mrs. T. revealed a good deal of anxiety regarding her daughter's attacks. This was intensified because the child had failed to respond to drug therapy as dramatically as many newspaper and magazine articles had led the mother to believe. She was a dynamic, tense person who was demand-

ing, ambitious, and easily irritated. At this time I learned that the family had recently moved into the San Francisco Bay area. Mrs. T. expressed great dissatisfaction with the attitudes and unfriendliness of people living in a large city—"I am a small town girl." In subsequent interviews, Mrs. T. revealed that she had set educational, as well as social, goals for her daughter. During these interviews, Mrs. T. was most critical of her community, her neighbors, and the schools, and in this period her daughter's attack rate soared. Mrs. T. brought out her disgust with previous physicians—"each had told her what to do—but nothing had helped." She told of attempting to set up a controlled environment, no radio, no comic books, no hilarious play, but all to no avail. At this point I attempted to define the limiting factors of the problem which she had not recognized previously, and pointed out that possibly her experience with us might also be fruitless in establishing control of K.'s convulsive attacks. Mrs. T. defined her feelings in working with her daughter, as she discussed "how humiliating it was to have your own daughter defy you, as well as possibly being one step ahead of you most of the time."

Interviews with K. revealed her to be an alert, warm, friendly, good-looking, 6-year-old girl. She started to make use of the toys and me immediately. During our first hour, she experienced six typical petit mal seizures. Her second interview was utilized in expressing an intense dislike for her 18-month-old sister, especially "when my mother gets after me." She demonstrated how she liked to crawl around on the floor, and talk like a baby, although she disclosed that her mother got "very mad" when she acted like her baby sister. At this time her attack rate soared and her drugs were increased: Tridione 0.3 Gm. four times a day and phenobarbital 0.015 Gm. three times a day. This change resulted in a decrease in seizures to eight to ten attacks daily. However, in two weeks, her mother reported a rise in the number of seizures to thirty or forty daily, in spite of her increased drug therapy. In an interview shortly after this, K. confided "I can do it any time I want." I accepted her statement and stated that she "could do it any time, as often as she wanted to, when she was with me." K. promptly had a voluntary seizure, calling my attention to her "rolling eyes." I remarked on her adeptness and asked her how she learned to do it. She then told how she had observed her mother telling "the doctor what I did. I can do it, too, and Mom gets excited." The next week, after sharing this information, K.'s attack rate dropped in number from thirty to forty daily to five or six attacks each week. The change was dramatic.

DISCUSSION

In many cases parents have reported children using their complaint of convulsive attacks in a most aggressive manner. They threaten a seizure if disciplined, or if denied some wish. Yet, the two cases here described are the only two, in my experience, who have voluntarily used their complaint. Their ability to imitate seizures has already been described, as well as the source of inspiration for imitation.

Both mothers were in need of better understanding of their children's disorder. In order to achieve this understanding, they had first to deal with their own feelings and attitudes regarding their daughters' complaints. Guilt, overprotection, and fear were blocking factors in the case of both mothers, which finally became resolved, at which time their roles as mothers were appreciated. Only then could they deal with consideration of their children's feelings and expressions of individuality.

Both children's voluntary attacks precipitated maternal anxiety and overprotection, which was satisfying and yet not satisfying to the child. Both children, in disclosing the voluntary nature of their seizures, indicated their feelings of security and willingness to accept the responsibilities of further separation and growth.

The first patient has been free from convulsive seizures since July, 1942. Her seizures responded to play therapy, as well as drug therapy. The drug therapy, namely, phenobarbital 0.03 Gm. three times a day, was slowly decreased in dosage. For the past three years she has been without medication and has been free from attacks. Her school progress has been satisfactory and she is popular and enjoys many friends.

The second patient continues to experience an occasional petit mal seizure. At present she is on Tridione 0.3 Gm. four times a day and phenobarbital 0.015 Gm. three times a day. She no longer experiences the number of seizures, which were so disturbing to her mother.

Lennox[4] has pointed out "that petit mal is the type seizure most easily precipitated by emotion." I know from these two cases that it can be imitated and used at will because of emotional or psychic upset. Bridge[5] has observed and has recorded in his recent book the influence of emotions in relation to convulsive disorders and their treatment. Airing, Lederer, and Rosenbaum[6] have suggested the possibility of psychogenic factors causing neuronal instability, increasing the susceptibility to seizures.

It is suggested that a medical history which revolves around a sympton or complaint factor (in this instance—convulsive attacks) should be elicited from the parent alone, and not in the presence of the child. Discussion of the history or complaint in the presence of the child has anything but a constructive effect on him. A physician, seeing parent and child separately, will be able to evaluate both participants' feelings and attitudes. Kanner[7] has stated "one immediately becomes aware of the important role which the complaint assumes, as the starting point and central focus in the approach to and the pursuance of any psychiatric difficulty of a child. The realization of its significance has forced itself upon one's mind, especially in a setting where there was an opportunity to gather the complaints, as expressed not only by the parents and the patients themselves, . . . but also, in every instance, by the physician who has referred the child."

SUMMARY

In the two cases presented, there is definite evidence of true convulsive state of the petit mal type and, in addition, voluntary attacks representing emotional complications. In both cases, the necessity for voluntary attacks has disappeared, as both patients and parents have accepted their own and the other individual's rights and feelings. Dawley[8] has clearly demonstrated the interrelated movement that exists between parent and child in therapy.

In the endeavor to practice good medicine, it is necessary and worth while to strive for the optimum in therapy. This goal calls for consideration of the psychologic as well as neurophysiologic aspects of the problem. In pediatrics this not only involves the patient, but also his family.

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PROBLEMS AROUND PSYCHOTHERAPY WITH CHILDREN

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THE SUBJECT of psychotherapy with children raises so many problems and questions in the mind of one with experience in a psychiatric clinic for children that it seems important to consider these problems even prior to considering something of what goes on between a psychotherapist and an emotionally disturbed child. It is not that the topic of direct psychotherapy of children is not in itself a sufficiently broad subject for discussion. Much has already been written[1, 2, 3] and remains to be written about its various unsolved problems. I am skeptical that a general discussion of the principles of the skill is very useful as a means for readers to acquire the skill itself.

In a sense, one could say that no one expects really to learn how to *do* something he has never done before simply from hearing someone else talk about how it is done, or from reading about it. Everyone knows that acquiring any skill requires practice, and generally, practice under supervision. After all, critics of this pessimistic attitude could say one can at least get some idea, a little general understanding, of some of the principles involved from reading or from lectures; and that when the principles are understood, they serve as guides and goals in actual practice. One can thus learn more quickly or more thoroughly than when one stumbles along uninformed, by trial and error.

Perhaps such critics are right. All they say is true of motor skills, or even perhaps of so-called mental operations involving symbols. However, in psychotherapy much more is involved. It is an operation probably more complex than any other. It involves the whole of oneself, all of one's attitudes. Very few people, if any, are entirely aware of all of their attitudes, or entirely in command of themselves and of all their feelings and reactions. But this lack of awareness does not preclude evocative reactions in others. This is true in all interpersonal situations, but particularly so in a psychotherapeutic situation where the patient-therapist, and therapist-patient response is the core of interaction. It serves as an obstacle, therefore, if the therapist has a problem similar to that of the patient. We shall discuss this crucial point at another point in this paper. In the meantime, this has served to indicate the author's reasons for pessimism in writing about psychotherapy.

The most obvious fact about childhood is its state of dependency, first its complete, then its relative, helplessness. We are concerned here with that inherent complex of strong feelings and urgent wishes for satisfaction in the young child which are in the power of the adult to grant or to deny. This complex of feelings has many facets and has received many polysyllabic names.

Based upon an address delivered to the Utah State Conference of Social Work at Salt Lake City, Utah, May, 1948, on the general topic of psychotherapy with children.

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One has heard of primary narcissism, of the attendant sense of magical omnipotence, of the dominance during this period of life of the pleasure principle, of the lack or deficiency in reality testing or ego formation, and so on. In simpler terms, perhaps in oversimplified terms, one could say that the young individual of the human species—in common with other living, moving things—is more or less completely egocentric while at the same time more or less completely unable to satisfy all these egocentric needs by his own efforts. He wants what he wants *when* he wants it, with little or no regard for the wishes or feelings of others. Some of these needs, of course, are absolute and must be satisfied or else he cannot survive. Other of his needs may be only partially or not at all gratified without danger to life, although always with quite inevitable effects on his later capacity to live happily with others of his kind. These other needs are, of course, for affection, warmth, and acceptance as belonging to the family with rights which receive just and generous consideration.

We are learning more and more thoroughly and precisely how devastating to the adult's sense of self-esteem (what we are now so often prone to call his *security*) are any deficiencies in this respect when experienced in these early years, and what a price his fellows in the community also pay for such defects. How to prevent or reduce such stunting of psychologic growth, what the ideal childhood experience is which promotes the full attainment of emotional maturity, the wise men of good will of all ages have known. The problem, therefore, is not one of lack of knowledge, nor of information. We know that few, if any, parents deliberately or with conscious malice deprive their children of essential affectional nutriment. They do for them only what they can do, no more and no less. They are, after all, the products not only of their own childhood experience with *their* parents, but also of all their later experiences with other persons. This means that they bring to their roles as parents such emotional strength, such emotional reserve, as they have been able to integrate from those experiences which have been helpful, considerate, and just. Unfortunately, they also bring to their parental functions all the products of their own stunting, malintegrating experiences with people. Unfortunately, no matter what compensatory attitudes they may muster to these derivatives of earlier conflict with others, in relation to their own children the same cycle between generations begins anew. Children, as one humorist quipped, despite what we teach them, insist on acting as we do!

The point of all this repetition of the obvious relation between the actual attitudes of parents and those of their children is simply that it is not only the child who needs psychotherapeutic help. The parents require essentially the same help when problems arise. This is the reason why psychotherapy with children does not mean, for me, what it seems to say. This is also one of the lessons of the experience of American psychiatric clinics for children. Simultaneous, concomitant therapeutic assistance to the parents of the neurotically suffering, or the problem child, is probably the most effective means of solving the problems which children and parents have with each other. There are often many obstacles and difficulties in the way of helping both of them, and not all of them are in the parents or the children.

Before going on to consider some of these obstacles, we need to clarify what is *not* meant by the statement that the most effective psychiatric help in parent-child problems is simultaneous concomitant psychotherapeutic work with both parent *and* child. It does *not* mean that no neurotically disturbed child can be helped by individual, direct psychotherapeutic work with him alone, that is, without the parent in concomitant treatment. There are numerous instances recorded in which therapeutic work with the child alone has been of considerable benefit. It is probable that most of the beneficial results of such an approach have occurred under special circumstances. Some of the factors which promote favorable effects of such direct treatment of the child alone are: the age of the child, the frequency and intensiveness of therapeutic sessions, and, what has been called by some, a "therapeutic milieu"[5] in which the child has lived during the treatment. The older the child, especially an adolescent, the greater is the possibility of therapeutic success without the concurrent treatment of the parents. It is also very probable that if the frequency and duration of treatment sessions with the child approaches that of classical psychoanalytic treatment of children, as described by Anna Freud and Melanie Klein: namely, up to four or five visits a week for many months or several years, the likelihood of helping the child resolve his neurotic conflicts is greater. Here too, however, we read in Anna Freud's writings[6] that the probability of therapeutic effectiveness also depends upon whether the parents are receiving psychoanalytic treatment themselves.

Finally, it has also been the experience of some psychotherapists of children that if the child is living in a specially staffed school or residential treatment center (in a personal environment, in other words, primarily oriented towards the therapeutic goal) direct psychotherapeutic work with him alone for a sufficiently long period of time is likely to be more successful.[5]

Merely reviewing these favorable circumstances for psychotherapy with children alone brings one back to the more common realities. The much greater number of children who need and are offered psychiatric assistance do not have parents with the financial means to place them in the usually expensive therapeutic milieus of special schools (even if there were enough of such schools or residential treatment centers), while defraying the costs of individual psychotherapy at the same time. A great number of disturbed children are still in the first decade of life, while a great many disturbed adolescents are also relatively still dependent upon their parents, emotionally as well as economically. Finally, the great numbers of children who are brought to the psychiatric clinics, the great shortage of adequately trained child therapists, the high cost of the service, not to mention the need to attend school which competes for the child's time, are all factors which tend to limit the number of visits of the child to the clinic to one, or at most, two per week. Under these circumstances, and because of the basic fact that the neurotic child is just one part of the neurotic network in the family relations, the most common practice of psychiatric clinics for children is to offer therapeutic sessions once a week with one, and occasionally with both parents, and generally make this a requirement of any therapeutic work with the child.

The difficulties and obstacles in helping both parent and child have been mentioned. Perhaps one of the chief difficulties is the therapist's lack of adequate training and clinical experience in working therapeutically with children. It is now rather generally recognized that training in psychotherapy (or psychoanalysis) with adults alone is not enough preparation, and most psychotherapists of adults readily admit their lack of skill or of readiness to attempt therapy of children. On the other hand, the writer's own experience inclines him to the view that therapeutic training and skill with children alone is often not the most adequate preparation either; at least, it is insufficient for treating some of the most severe problems in parent-child relations. Too often one sees such children considered to suffer from some obscure organic disease, which rarely materializes on thorough study, when the clinic staff has been unable to recognize or to treat adequately the concomitant personality problem of the parent.

In this connection, the frequent custom of assigning the parent to a psychiatric social worker, while the clinic psychiatrist works with the child in the playroom sometimes proves to be a source of difficulty. If the worker is competent by training and experience to deal with adult neurotic disorders, such a division of labor is an effective arrangement. However, if the worker is less skilled psychotherapeutically than the psychiatrist, the worker often has the more difficult clinical burden. If the psychiatrist is inadequately trained or inexperienced with adults, he cannot be of much assistance to the psychiatric social worker in his supervision of the therapy of the parent in the more difficult cases.

To speak of the interview of the social worker with a parent in these circumstances as "therapy" rather than "casework" often brings protest not only from many psychiatrists, but from psychiatric social workers as well. There are many arguments on both sides of this debate as to whether the work of a psychiatric social worker in a clinic setting is "therapy" or "casework." Not only semantics, but professional prestige and its attendant anxieties are inextricably involved in this endless debate, and we shall not enter into it further, except to make one point.

This point might be listed as another of the obstacles which exist in the way of effective psychiatric service to parents and children. If neither the psychiatrist nor the psychiatric social worker is convinced that probably all personality problems and disorders are the result of malintegrating experiences with the significant persons during the most susceptible periods of life, he may be either unclear about the actual role of the parent in the child's difficulty, or be less precise in his therapeutic work with both of them. Many cases are left without help because of the existence of the foggy notion that the work with the parent needs to be only some sort of casework, with a "focus" of "support" to the parent as a parent, rather than therapy with a person having neurotic difficulties which may be most evident in his relation with his child. The neurotic entanglement of the parent with the child requires as expert psychiatric skill for its resolution as does the child's reciprocal neurotic

involvement with his parent. This means, among other things, that mere "advice," "suggestions," or "education" are not of very much value, even though the parent begs anxiously or demands with hostile insistence for "concrete" help from the expert. We have often seen such suggestions carried out literally, but with the same attitude as that which brought about the problem in the first place, with the parent returning to report the failure of the therapist's advice. "Support," "advice," or "education" will often do little to modify the balance of psychologic forces within either the parent or child unless rational and precise therapy of the parent's deep conflicts is undertaken.

As an example illustrating some of these statements, the following brief excerpt from an actual clinical experience may be useful:*

CASE REPORT

Mary is a 10-year-old girl who lives with her mother in an apartment house in which live her mother's parents, and with her mother's brother and his family. It is the same home where her mother was reared. Her brother, John, a veteran, is fifteen years older than Mary and is attending college in a near-by town. Her father is a man who is described as a pleasant, friendly person who cannot resist gambling, and who has been in jail three or four times because of check forgeries to pay his gambling debts.

Mary is said to be a very bright, willful child who insists on getting her own way, and who has been "spoiled" by her father, her grandparents, her brother, and her aunts and uncles, since she is the only girl child in the family.

When Mary was first seen over a year ago, her father had just started a year's prison term because of another forgery. Her mother, a vacillating and indecisive person, was having a good deal of trouble with her. Mary would not mind, and any attempts to make her do such things as wash or comb her hair would cause her to yell and scream far into the night. Strangely enough, Mary had no difficulty at school. She was an outstanding student scholastically, and she revealed none of the behavior which she showed at home. It was quite evident that the main area of disturbance lay in the relationship between Mary and her mother.

Mary was referred for hospital treatment because of her refusal to eat, dress, and keep clean. She was admitted as an emergency one evening at the suggestion of psychiatric physicians who had seen her at home, and without adequate discussion of the problem with the mother prior to admission. After three days an uncle took her home for a holiday party and the family was unable to return her to the hospital. After this attempt to start a treatment program failed, ten months passed during which time Mary was seen by other clinics until she finally became a ward of the Juvenile Court because her early morning screaming had forced the neighbors to complain to the police. Plans were being made to send her to the children's division at the State hospital, since, according to the probation officer, "All the agencies in town are washing their hands of Mary and her mother, and the neighbors are clamoring." In the meantime, the mother had divorced the father. Finally, because of pressure by external agencies, the mother was forced to make application for help, but Mary refused to visit the clinic, so it was decided to work with the mother alone.

In the past six months, without having seen Mary once, there were only two calls from the probation officer in response to complaints by neighbors, and these disturbances occurred in the first three months. Mary's mother began to

*The author is obliged for this summary to a colleague, Dr. Samuel Susselman, who was directly responsible for the clinical work with the mother.

understand something about her own rivalry with her daughter for attention and affection from the rest of the family. She also became aware of the fact that she had been so overjoyed at her son's return from foreign service that she had to some extent neglected Mary, which Mary resented bitterly. Mary always created a major scene when her brother visited home, so he was forced to remain away. The mother used to visit him surreptitiously at college without Mary's knowledge. She couldn't even mention his name at home without fresh outbursts from Mary. The reader may be spared the many other details.

About two months ago, the father was released from jail and is attempting a reconciliation with his wife. In the meantime he is being allowed to see Mary who is very devoted to him.

Recently he discussed his son, John, with his wife in Mary's presence. She immediately started upon a characteristic violent tantrum. The father took one look at Mary and said in a firm, angry and unequivocal tone, meaning every word, "If you don't stop that yelling, I'm not going to like you." To the mother's amazement, Mary stopped at once. The father seemed to mean business. Twice since then they have discussed the son and each time the father and daughter looked fixedly at each other for a moment, and that was all there was to it. The mother finds such a simple and definite display of her emotions difficult. She is so bound up in her own insecurities and anxieties in relation to Mary, that she would have been confused by mere advice. The mother has progressed sufficiently as a result of therapy in the past six months, however, that Mary has been no great problem recently. She has continued to do well at school and the necessity for institutionalization seems remote. The contrast between the mother's and father's ability to deal with Mary is a classical example of such a situation as one might meet in a psychiatric clinic.

This brings us to another of the obstacles which interfere with adequate psychotherapeutic work with parents and children. Persons attracted to therapeutic work with children's problems often have a basic overidentification with the child. This attitude seems to imply that the parent is the enemy of the child; that the parent should be shamed or subtly coerced into more generous and kindly treatment of the child; or that the child must be protected against the bottomless hatred of the parent. Most parents who bring their children to psychiatric clinics are already self-critical, although defensive, and this overidentification of the therapist with the child only tends to increase the parents' conflict.

This overidentification is of little help to the child since it often encourages him to self-destructive rebelliousness against the parents, either by impulsive behavior or an increase of anxiety, or both. This type of interaction between the therapists and their respective patients can hardly be graced with the name of psychotherapy.

Except for two comments, we shall not consider at any further length the sources of such overidentification of the psychiatric clinicians with children. Most adults have some unresolved conflicts stemming from childhood. This sometimes manifests itself in *irrational* degrees of sympathy with the underdog, with the weaker of two opponents, and particularly with children against their parents. Such sympathy, in its irrational part, is an expression of our own unsolved rebelliousness which gains less guilty release for the sake of another. The actual strength or favorable aspects of the apparently oppressed person (in our case, the child's situation) is lost and both his assets and potentiality for growth are

underestimated. One's own anxiety is of little help to the one for whose sake such unconsciously hostile efforts are made. This leads to the second point: that rational psychotherapy by a person with such unresolved and usually unconscious conflicts is difficult, if not impossible.

Either such a therapist should avoid any seriously intensive efforts at psychotherapy with children or their parents, or seek psychotherapeutic help for himself as the initial preparation for his work. Such reasons have led to the psychoanalytic school of psychiatrists to require personal analysis as the preliminary to any further training for skill in psychologic treatment of others.

What has been said about the obstacles in the therapists, does not imply that no difficulty exists within the parents or children which might militate against successful psychotherapeutic work. It is only that unless those within the therapists are minimized, the chances of reducing the obstacles within the patients are decreased to that extent. There are many difficulties on the patient's side in even seeking psychiatric help.

The psychotherapist has much greater difficulty than any healer of organic disease because, as Dr. Gregory Zilboorg[7] says, when it comes to emotional disorder, so many people are not only uninformed and ignorant of its nature and causes, but also believe with a peculiar tenacity in many things about it which "just ain't so." Even for an experienced and skilled psychotherapist it is extremely difficult to remove some of these erroneous beliefs—in themselves, rationalized delusions serving to reduce anxiety—and to permit a sufferer from a neurotic disorder to consider psychotherapy as a possible source of relief. This difficulty is particularly great in the case of parents of disturbed children. The child's disordered behavior and feelings are his adaptation to the parent's own emotional problem. Part of themselves has unconsciously and unwittingly created the child's attitudes, and obtains gratification from it. The parent, concerned with bringing about the change in the troublesome part of the child's behavior and not with the more fundamental reorganization of the child's self-regard and basic attitudes, overlooks the basic need for change in his own self-organization. Thus, the problem of helping the parent to consider seriously, and accept therapy for himself at the same time, is generally the first and most formidable obstacle. Even when the work has begun, it takes almost greater skill in helping the parent continue, when treatment begins to imply changes both in the child and parent which are frightening in themselves.

Without further elaboration of this clinical problem, let us consider a few technical aspects of psychotherapeutic work itself with children. Direct psychiatric treatment of children, during the past fifteen years has come to be known as "play therapy," especially with children between the ages of 2½ or 3, and 8 or 9 years. The technique using such toys as dolls, clay, finger paint, blocks, and other playroom material stems from the much more intensive therapeutic work known as "child analysis" which was developed primarily in Europe, especially in Vienna, by Anna Freud. Such pioneers hit upon the idea that play was the natural medium of expression for the child, rather than the collaborative self-revelation in speech as with adults. The less intensive, less frequent sessions of psychotherapy of children in American clinics has been

said to be different in some important respects from the classical psychoanalysis of children. In other respects, the differences with which people practice are enormous. These differences are often gross misconceptions. A friend[8] writing on the subject says that many adults play *with* children but they do not do anything resembling psychotherapy.

Dr. Frederick Allen,[9] one of the most expert of American child psychiatrists, has said recently that in an important sense there is no such thing as *play therapy*, meaning that unrestricted freedom in the playroom has little in common with a serious effort to allow the child to experience himself in a new kind of relation to an adult. Play during therapy is a drama which unfolds before the therapist with his skillful participant observation. The therapist not only allows but quietly encourages the child to write the script.[8] And all this is for the neverforgotten purpose of first comprehending the child's feelings, his usually uncomfortable solutions to his conflicts, and then helping the child to find new and happier, more successful resolutions of his dilemmas. The over-all goal is finally that the child acquire a new spontaneity, less fear of his own impulses, a new command of himself, and a more solid self-respect as a person. The details of how this may be done, what patience is required for the child to integrate such a new self-regard at his own pace, what intuitive perceptiveness is required to keep pace with the nuances in the constantly changing feelings in what is often known as the transference, how it all may be helped to end in a healthier parent-child relation at home, are things to be learned only in the *practice* of the skill. And that practice needs close, prolonged, and expert supervision of the trainee in individual sessions.

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THE SIGNS OF BRUDZINSKI AND OF KERNIG

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SELDOM does one see a textbook on pediatrics in which the signs of Brudzinski and of Kernig are not mentioned. There is scarcely a hospital chart of a child with meningitis without the entry: "Neck rigidity, Brudzinski and Kernig—positive." These signs are often termed "test," "phenomenon," "reflex," and are so popular as to be frequently referred to simply as "Brudzinski," "Kernig." They have achieved the familiarity of "Babinski," "Romberg."

What is the basis for these signs? The textbooks usually describe them in detail and enumerate the various diseases in which they are found. Little, however, has been written about the mechanism of the signs, and even this little is controversial and confusing. The purpose of this paper is to discuss the pathophysiology of the signs of Brudzinski and Kernig, their relationship to each other, and their integration with signs based on the same physiologic principle.

Brudzinski described several signs found in meningitis, all of which bear his name. Here, only the "Brudzinski neck sign" will be considered. It will be referred to as the Brudzinski sign. It was first described in 1909 by Brudzinski,[4] a pediatrician in Warsaw. It consists of automatic flexion at the hips and knees when the head of the child is passively flexed.

Kernig,[11, 12] a neurologist in St. Petersburg, described his sign first in 1882 and again in 1884 in a Russian journal. It was then described in greater detail in German journals in 1884 and in 1907.[13, 14] The sign is demonstrated by raising one or both legs of the supine patient. The premature limitation of this passive movement by the contraction of the hamstring muscles constitutes a positive Kernig sign.

The Brudzinski sign is by no means pathognomonic for meningitis, as was first assumed. It can be elicited in cases of spinal cord tumor, myelitis, prolapse of the intervertebral disc, tetanus, and many other affections of the spinal cord and its roots. The motor manifestations are not confined to the lower extremities. Flexion of the head, under conditions causing the Brudzinski sign, is accompanied not only by flexion of the lower limbs but also of the forearms. A simultaneous involuntary head retraction occurs, and can be felt on palpation. The Brudzinski sign has sensory manifestations in addition to its motor manifestations. In meningitis, as well as in many affections of the cerebrospinal axis, localized or diffuse painful sensations may be experienced by the patient when the head is bent. Some of these affections are: tumor of the cauda equina, "high sciatica," radiculitis, cerebrospinal syphilis, trauma to the cervical cord, multiple sclerosis, poliomyelitis.

The same may be said of the Kernig sign: (1) It is not pathognomonic for meningitis, as is often maintained, but is found in many of the other conditions

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in which the Brudzinski sign is positive. (2) The motor manifestations are not restricted to the lower extremities, inasmuch as a simultaneous flexion of the forearms may occur. (3) The manifestations are not only motor, but sensory as well, with pain most often felt in the region of the sciatic nerve.

The symptom of pain in the Kernig sign is significant because it brings this sign into relationship with the famous Lasègue sign. It is of passing interest that in textbooks and medical encyclopedias the statement is made invariably that Lasègue[15] described his sign in the now classic paper, "Considérations sur la sciatique," published in 1864. He did not. His paper contains nothing pertaining to this sign. It was, in point of fact, Lasègue's pupil, Forst,[9] who, on the basis of Lasègue's teaching, first described the sign in his doctoral thesis in 1881. This sign is positive when, with the same manipulation as in the Kernig test, pain is felt in the area of the sciatic nerve. There are numerous modifications of the Lasègue sign, but the mechanism in all is fundamentally the same. It is understandable, therefore, why many use the term Lasègue-Kernig sign, or Kernig-Lasègue sign.

What has been said about the Kernig sign applies equally to the Lasègue sign. (1) A positive Lasègue is by no means pathognomonic for sciatica, the condition in which it was first described. A Lasègue-Kernig sign has, for instance, been found by Foerster[8] in the following conditions: meningitis, subarachnoid hemorrhage, epidural hemorrhage, tumor of the cauda equina, radiculitis, cystic serofibrinous arachnoiditis, spina bifida, and in other irritative conditions of the lumbosacral roots. Often, a positive Lasègue is found in poliomyelitis during the infectious stage. (2) In Lasègue there are motor as well as sensory phenomena, reminiscent of those found in Kernig. In his textbook, Wilson[23b] defines Lasègue as follows: "passive extension at knee with hip flexed eliciting pain down the nerve and defensive contraction of hamstrings." (3) A patient may experience, on the elicitation of a Lasègue sign, pain and paresthesias in areas remote from that of the sciatic nerve.

The close relationship between the signs of Brudzinski, Kernig, and Lasègue makes it understandable why in sciatica, for instance, all three may be positive. The question, therefore, may be raised as to whether the basic mechanism underlying all of these signs may not be the same.

Many of the hypotheses offered to explain this mechanism are unsatisfactory and confusing. Among others, the following factors have been cited as possible causes for the appearance of the signs of Brudzinski and Lasègue: cortical irritation, a reflex arising from the nerve endings of the meninges, an abnormally increased stretching reflex, proprioceptive stimulation coming from the muscles of the neck, an increased reflex of the lower spinal cord, pathologic associated movements, an affection of the corpus striatum, and an increase of intracranial pressure. Brudzinski[5] wrote vaguely of "muscular hypertonia and of some physiologic preponderance of the extensors of the back and neck over the flexor muscles of the lower extremities," and again, of the "influence of the irritation of the lower lumbar roots, of circulatory disturbances of the brain, of the fluctuations in intracranial pressure." The most widely accepted explanation for the

Brudzinski and Kernig signs is that they belong to a group of tonic neck reflexes. This view is held by such men as Wilson,[23a] Purves-Stewart,[18] Magnus,[16] and has found its way into modern textbooks. Grinker[10] states that the Brudzinski sign "represents a tonic neck reflex in the partially decerebrate state." Wechsler[22] says: "Brudzinski sign is, in my opinion, also a tonic neck reflex."

None of these hypotheses is satisfactory or complete. None take into consideration all of the following points: (1) These hypotheses do not explain the great variety of morbid conditions in which the signs occur, and none of these signs is pathognomonic for a single disease, as was assumed by those who first described them. (2) The motor manifestations are more intensive and extensive than the discoverers of the signs perceived. (3) In neither sign are motor or sensory manifestations found exclusively, as is often claimed, since each sign may show various combinations of both motor and sensory phenomena, and in varying degrees. (4) The hypotheses fail to explain those motor and sensory phenomena which may occur in remote areas of the body, not directly affected by manipulation for the tests.

With regard to the hypothesis which sees in the Brudzinski-Kernig a tonic neck reflex, it may be said further that tonic reflexes are not accompanied by sensory phenomena. In meningitis the Brudzinski and Kernig signs are seen in the early stages of the disease, often within twenty-four hours after onset, and this is much too short a period for the establishment of the brain stem lesion required by the tonic reflex hypothesis. On the other hand, in cases of hemiplegia, where tonic reflexes might be expected, the Brudzinski sign is absent on the paralyzed side, as, for example, in meningitis with hemiplegia.

It would appear unnecessary to invoke complex cortical, subcortical, or other reflex mechanisms in order to explain the Brudzinski and Kernig signs. A more simple explanation can be given in terms of mechanical factors affecting the spinal cord when the head is forcibly flexed forward. Néri[17] demonstrated in experiments on cadavers that vigorous flexion of the head may produce an elevation of the medulla oblongata up to 3 or 4 millimeters. Schambouroff[19] was able to "prove on cadavers that enforced flexion of the head to the chest is associated with an upward motion of the spinal cord of nearly 1 cm. in the lumbar region."

The anatomical investigations of Deutsch[7] and Bragard[2] demonstrated that it is the stretching of the sciatic nerve in the Lasègue test which is effective. Sjöqvist,[20] on the basis of experimental studies, said: "It is indeed almost amazing to observe the wide excursions made by the root upwards and downwards when the knee is flexed and extended." He concludes that "the sign of Lasègue is neural in origin and produced by purely mechanical factors."

Other nerves and plexuses may be effectively stretched by certain manipulations. Charpy[6] found that in turning the head of a cadaver to one side, as in the so-called "shaving position," the brachial plexus on the opposite side becomes taut like a violin string. Bikeles[1] could demonstrate that when the brachial plexus is stretched maximally in meningitis or polyneuritis, phenomena analogous to the signs of Kernig and Lasègue appear.

In the Brudzinski sign, the spinal cord is stretched, and the pull is transmitted along its whole length and involves its most distant roots. In the Lasègue sign, the stretching first affects the sciatic nerve, then the lumbosacral plexus, and the pull may be transmitted to the spinal cord. When the meninges of the spinal cord and its roots are inflamed or so diseased as to impede their free movement, pain results. This is felt in the area of the affected meninges and may be very severe.

Naturally, the patient tries in every way and by every means to relieve the pain. He assumes that position which is most comfortable to him—(a) to decrease the stretch of the spinal cord and its roots; and (b) to minimize the effect of stretching when it does take place. In meningitis, for instance, the patient lies with his head retracted, the spine lordotically curved, and the legs flexed, a position which serves to relax the stretch of the cerebrospinal axis. Flexion of the legs seems to be particularly helpful to the patient. It apparently compensates for the mild stretching of the cerebrospinal axis incident to flexion in the hip joint. Textbook pictures of children with meningitis illustrate this position very clearly, i.e., retraction of the head, the curving of the spine, and flexion in the hip and knee joints (Bregman[3]). These positions are exactly opposite to those passively achieved by manipulation for the tests of Brudzinski, Kernig, and Lasègue.

In pediatric literature, in addition to neck stiffness commonly associated with meningeal irritation, two other signs of the infectious stage of poliomyelitis are often mentioned: the "spinal sign" and the "Amoss sign." In the spinal sign, the child is unable to touch his knees with his lips or rest his head on his knees while sitting up in bed with his knees flexed. In the Amoss sign, the child, while sitting up in bed, shows a predilection for supporting his weight in a characteristic position, which consists in stretching his arms backward and outward in such a way as to form a triangle with his coccyx. Both signs are manifestations of the same protective reaction on the part of the patient who tends to keep his spine extended, since flexion produces pain.

These positions may be termed prophylactic measures, which serve to anticipate and avoid any possible stretching of the cerebrospinal axis. When nerve stretching is produced by passive movements, the child tries to minimize its effect. In the Brudzinski maneuver, he first counters by tightening the muscles which retract the head and thus prevents or limits head flexion. Since the passive head flexion cannot be fully prevented, the patient then tries to minimize the effect of stretching on the *upper portion* of his cerebrospinal axis by shortening, and thus relaxing, the *lower portion* of this axis. This is best achieved by flexion of the lower extremities, the position assumed in meningitis. In the Kernig-Lasègue sign, the patient reacts in the same way—he reacts with pain since raising the extended legs stretches the nerves and causes pain (Lasègue). He reacts also by "defensive" contraction of the hamstring muscles (Kernig). Sometimes the patient makes further attempts to relax the cerebrospinal axis by retraction of the head and flexion of the forearms.

These prophylactic and defensive positions are genuinely protective. Mechanically and physiologically, they are appropriate, sound, and under the given conditions maximally effective. In all the assumed positions, the fundamental mechanism is the same: counteraction to the stretching of the nerve tissues to avoid pain.

In some tests involving the stretching of nerves, the element of pain predominates, while in others motor phenomena are more prominent. Many "signs," "symptoms," "reflexes," and "tests" to be found in the literature are basically nerve-stretching tests. Of these, the Brudzinski, Kernig, and Lasègue signs are the three most popular.

Similar phenomena are seen in stretching of the nerves, mixed or sensory in character, where the effect is limited to the nerve only, and does not reach the spinal cord. This applies to single nerves of the brachial or lumbar plexus, and particularly to the superficial branch of the radial nerve (Wartenberg[21]), the cutaneous nerve of the thigh, the genitofemoral nerve, the femoral nerve, etc.

Elsewhere I have said: "To no other stimulus does the diseased nerve react so early and so intensively with pain as to stretching." A positive nerve-stretching test is a constant, very early and very late sign of a mixed or a sensory neuritis. This applies not only to isolated stretching of the peripheral nerves but also to stretching of the spinal cord and its roots. The reaction of the patient to such stretching may have manifold and remote manifestations. It may consist of pain alone or in motor maneuvers designed to protect the nerve tissue and to minimize the effect of the stretching. These motor reactions of the patient cannot be classified as reflexes in the correct sense of the term. They are automatic, conscious or unconscious, protective and defensive reactions to pain.

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